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TREATMENT OF UNEXPECTED CARDIAC ARREST BY EXTERNAL ELECTRIC STIMULATION OF THE HEART*

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CARDIAC arrest may occur unexpectedly during various diagnostic and therapeutic procedures, particularly under anesthesia. Though infrequent (1 in every 500 to 5000 operations[1,2]), each accident is a catastrophe. Despite the wide, active interest in this problem current therapy is too often unsuccessful.

The commonly recognized mechanisms of cardiac arrest are ventricular standstill and ventricular fibrillation; standstill is the usual cause. In a compilation of 1200 cases of cardiac arrest, Stephenson et al.[3] placed the occurrence of standstill at 88 per cent. Of 141 cases[4-8] in which the mechanisms were specifically diagnosed by electrocardiograms or direct observations of the heart, ventricular standstill occurred in all but 1. A third mechanism, complete atrioventricular block with a normal sinoatrial rhythm and a very slow ventricular rate, may occur during cardiac surgery and may cause cessation of circulation; 3 cases have come to our attention.[9-11]

In recent years immediate thoracotomy with cardiac massage has become generally accepted as the primary measure in the management of unexpected cardiac arrest. Thoracotomy is recommended at the first suspicion of arrest (disappearance of arterial pulsations), primarily to effect immediate restoration of circulation by massage of the heart. In addition thoracotomy permits confirmation of the diagnosis of arrest of the heart and determination of the cardiac mechanism causing the arrest. Blood flow to the heart and brain must be restored within three or four minutes if cardiac and cerebral function is to return unimpaired. In view of this desperate urgency, the recognized risk of occasional unnecessary thoracotomy for conditions other than cardiac arrest has been accepted by many surgeons.[8,12]

At best, however, thoracotomy with cardiac massage is hazardous and formidable. The frantic urgency with which cardiac massage is often carried out adds to its risk. It imposes the strain of a major procedure upon a desperately ill patient. Incision of a cardiac chamber,[13] rupture of the heart,[14] serious intrathoracic hemorrhage[15] and sepsis[16] have been reported. Fatal delay often occurs because of failure to recognize the arrest immediately and because of unfamiliarity and hesitation in undertaking the procedure. Finally, arrest may recur after the chest has been closed; then, repeated thoracotomy is all the more formidable.

Although many patients have been saved by this procedure, in view of these considerations it is not surprising that the rate of complete recovery is low: 12 to 67 per cent in several small series of cases,[4-8,13] but only 28 per cent[3] and 34 per cent[17] in two large compilations.

The measures of pounding the precordium, puncturing the heart with a needle and injecting drugs into a cardiac chamber are often tried before thoracotomy, but are much less effective. These procedures are simple, readily applied and require little time. They carry the risks of hemorrhage[18] and ventricular fibrillation,[13] which risks are relatively slight compared to those of thoracotomy with massage.

The present report deals with the application to the problem of unexpected cardiac arrest of a new resuscitative procedure that we have developed: it is a technic of external electric stimulation of the heart that terminates ventricular standstill and maintains an externally paced ventricular rhythm for as long as necessary. This technic cannot terminate ventricular fibrillation nor stimulate effective beats

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in the severely anoxic heart. The electric stimulator functions like a natural intracardiac pacemaker but is under complete control. The instrument is portable, easily applied and clinically practicable.

This approach to the problem of cardiac arrest has been applied[18-21] to the treatment of Stokes–Adams disease, reflex vagal standstill, standstill due to digitalis intoxication and now to unexpected arrest occurring under anesthesia.

Case Reports

Eight successful cases of cardiac resuscitation from unexpected arrest by electric stimulation of the heart are reported here. The cases occurred during various procedures — 7 during surgery, and 1 during pericardiocentesis. The cardiac arrest was terminated in each case by the electric pacemaker so that thoracotomy and cardiac massage were not necessary. Five patients recovered completely; 2 died of unsuccessful cardiac surgery, and 1 died eight hours after operation.

One of these patients (Case 7) was observed by us personally. The other cases have been described in personal communications from the physicians concerned and are reported here briefly with their permission.*

Four episodes of ventricular standstill after abdominal surgery, with immediate resuscitation in each by external electric stimulation, followed by complete recovery:

Case 1.[22] A 48-year-old machinist suffered a massive gastrointestinal hemorrhage, for which a prolonged abdominal exploration was performed. Preoperative medication included atropine, 0.3 mg. (1/200 gr.), given at 10:45 a.m. Anesthesia was started at 12:05 p.m.; the agents were thiopental sodium (Pentothal) (1.4 gm.), curare (23 ml.), nitrous oxide and oxygen. The pulse and blood pressure remained stable until the end of the operation; during closure, at 4:45 p.m. and again at 5:12 p.m., the pulse and blood pressure disappeared suddenly but returned quickly without treatment. Because of these episodes an external cardiac stimulator was made ready.

At 5:23 p.m. there was sudden cardiac arrest, with absent pulse, blood pressure and heart sounds, dilated pupils and cyanosis. The external electric cardiac pacemaker was applied within 3 minutes, and in a few seconds restored a normal pulse and blood pressure. After 5 minutes electric stimulation was stopped, and a spontaneous cardiac rhythm continued.

Fifteen minutes later (5:46 p.m.) the heart stopped suddenly again, whereupon external electric stimulation restored the pulse and blood pressure immediately. Stimulation was continued for 30 minutes; when it was stopped the heart continued to beat spontaneously.

Thirty minutes later (6:46 p.m.) the patient was moved from the operating table to his bed. With the movement there was a 3d episode of cardiac arrest. It was immediately terminated by the electric pacemaker. Stimulation was continued for 10 minutes; when it was stopped the heart continued to beat spontaneously.

At 7:16 p.m., within a minute of the patient's removal to his room, cardiac arrest occurred for the 4th time and was again immediately terminated by external electric stimulation of the heart. One hour later the patient was responsive and oriented and showed no residual neurologic damage. He recovered completely and returned to full-time work.

No drugs were administered during these 4 episodes of cardiac arrest. The only therapy was the external cardiac pacemaker.

Complete heart block and ventricular standstill after cardiac surgery, with external electric stimulation for 63 hours, followed by complete recovery:

Case 2.[23] A 30-year-old man had combined mitral and aortic valvulotomies. After operation complete heart block appeared, and the idioventricular rate slowed progressively. Ten hours later, when the rate had slowed to 25 per minute, the patient became comatose. The external electric cardiac pacemaker was applied at a rate of 65 per minute, and he became conscious and alert almost at once. External stimulation was necessary for 63 hours to maintain adequate circulation. "At various times the pacemaker was turned off: the heart stopped beating and death-like coma occurred within seconds. After periods as long as 15 seconds, the pacemaker was restarted and at once alert consciousness returned."[10] Normal atrioventricular conduction and spontaneous ventricular beats then returned, and he recovered completely.

Two episodes of cardiac arrest after thyroidectomy in a patient with Stokes–Adams disease, with immediate resuscitation in each by external electric stimulation, followed by complete recovery:

Case 3.[23] A 57-year-old woman with complete heart block had three Stokes–Adams attacks 12, 6 and 5 months before a left-sided subtotal thyroidectomy performed because of thyroid enlargement with tracheal obstruction.

Atropine, 0.4 mg. (1/150 gr.), was given 1 hour before anesthesia, and the electrodes of a cardiac pacemaker were applied to the chest. Anesthetic agents were thiopental sodium (Pentothal), 0.6 gm., decamethonium bromide (Syncurine), 3.5 mg., and ether by endotracheal tube. During the operation the pulse remained stable at the preoperative range of 35 to 40 beats per minute.

After the hemithyroidectomy a tracheotomy was performed to ensure adequate oxygenation. After the tracheotomy tube had been put in place, coincident with movement of the patient's head, the pulse and respiration suddenly disappeared, and the pupils became widely dilated. Approximately 20 seconds later the cardiac pacemaker was turned on, and there was an immediate return of arterial pulses synchronous with the electric stimuli at a rate of 70 per minute. After 1 minute spontaneous respirations returned; electric stimulation of the heart was stopped, and the previous slow idioventricular rhythm reappeared.

One minute later the pulse and respirations again stopped. The external pacemaker terminated this 2d episode of cardiac arrest immediately. The cardiac pacemaker was kept in emergency readiness during the postoperative period, but further episodes did not occur and the patient recovered completely.

Cardiac arrest after procaine amide during cholecystectomy, with resuscitation by external electric stimulation, followed by complete recovery:

Case 4.[24] A 67-year-old woman underwent cholecystectomy. Anesthesia was carried out with thiopental sodium (Pentothal) followed by endotracheal administration of cyclopropane and oxygen. One hour and 10 minutes after induction bigeminy due to frequent ventricular premature beats occurred. Procaine amide hydrochloride (500 mg.) was given intravenously, and an external electric pacemaker was attached.

After a few minutes of procaine amide administration, cardiac and respiratory arrest suddenly occurred; the aortic pulse was absent, and cardiac activity could not be felt through the diaphragm. After 45 seconds of arrest the cardiac pacemaker was turned on, and the aortic pulse returned immediately. For 5 minutes circulation depended upon the external pacemaker: the pulse rate varied with the rate of stimulation, and the heart beat stopped when stimulation was momentarily interrupted. At the end of

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this time spontaneous cardiac activity returned, and external stimulation was then stopped.

The patient made an uneventful recovery and showed no ill effects.*

Ventricular standstill during gastrectomy, with immediate resuscitation by external electric stimulation and survival for 8 hours:

CASE 5.[26] A 45-year-old man underwent gastrectomy for carcinoma of the stomach with massive, persistent hemorrhage. Before operation he required multiple transfusions, and the external electric pacemaker was attached because of his poor general condition. The operation was carried out under thiopental sodium (Pentothal) intravenously and continuous spinal anesthesia. At the end of 2 hours as the surgeon was preparing to resect the stomach, he observed sudden cessation of aortic pulses and of cardiac movements transmitted through the diaphragm. At the same moment the anesthetist noted that the blood pressure was unobtainable.

Cardiac puncture, intracardiac injection of epinephrine and cardiac massage through the unopened diaphragm failed to produce cardiac contractions. Without further delay, the cardiac pacemaker was turned on. There was an immediate return of effective cardiac beats: the surgeon noted aortic pulsations, and through the diaphragm he could feel the heart beat synchronous with the electric stimuli; at the same time the blood pressure returned to its previous level. After a few minutes electric stimulation was stopped, and the heart continued to beat spontaneously.

The operation was then completed without further interruption. The blood pressure was maintained at an adequate level, but eight hours later the patient died suddenly. The cause of death was not determined.

Cardiac arrest during pericardiocentesis, with resuscitation by external electric stimulation, followed by complete recovery:

CASE 6.[25] A 68-year-old woman suffered sudden cardiac arrest during a pericardiocentesis after the removal of 400 ml. of fluid. Within 2 minutes external electric stimulation was applied, resuscitating the patient promptly. After 15 minutes, stimulation was stopped, and she recovered from this episode without ill-effect.

Repeated ventricular standstill after cardiac surgery, with cardiac resuscitation twice by external electric stimulation and with a fatal outcome:

CASE 7. A 12-year-old girl underwent surgery for tetralogy of Fallot. Immediately after the chest had been closed, cyanosis increased, and marked cardiac slowing and ventricular standstill occurred. On 2 occasions, cardiac puncture restored effective ventricular activity temporarily. During a 3d period of arrest external electric stimulation produced ventricular beats with synchronous peripheral pulses, followed by temporary return of a spontaneous supraventricular rhythm (Fig. 1). Arrest recurred for a 4th time, and the external pacemaker again produced effective beats. Spontaneous ventricular activity did not reappear, however, and external stimulation had to be continued. After 10 minutes the blood pressure could not be obtained, the stimuli became ineffective, and the patient was pronounced dead.

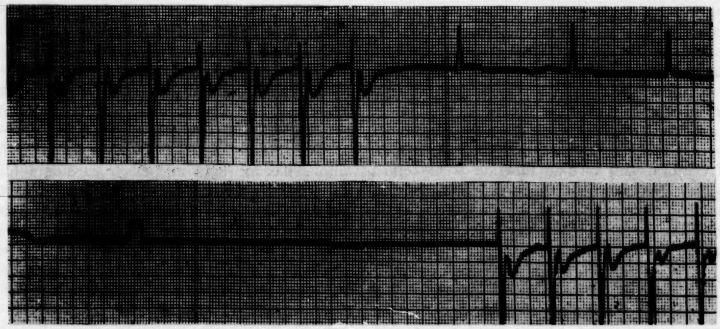

FIGURE 1. *Resuscitation from Ventricular Standstill after Cardiac Surgery in Case 8. Effective electric stimulation during ventricular standstill is followed by spontaneous cardiac beats* (A). *An episode of ventricular standstill is terminated by effective external stimulation* (B).

Autopsy showed that a small bronchial artery anastomosing with a pulmonary artery had been ligated, thus reducing further the already critically limited pulmonary circulation. This reduction in pulmonary blood flow produced marked anoxia manifested by the severe postoperative cyanosis; presumably, the anoxia led to the recurrent cardiac standstill and the fatal outcome.

Ventricular standstill during cardiac surgery under hypothermia, with cardiac resuscitation by electric stimulation applied directly to the heart and with a fatal outcome:

CASE 8.[27] A 3½-month-old boy with a congenital cardiac anomaly underwent cardiac surgery under hypothermia. Ventricular standstill occurred, whereupon electric stimulation was applied directly to the heart and produced effective ventricular beats for 2 hours. An adequate circulation could not be effected by the surgical procedure, and the patient died.

DISCUSSION

These experiences indicate that external electric stimulation can resuscitate the heart from arrest occurring unexpectedly under anesthesia during various procedures, just as it does from the other types of cardiac arrest. The technic has been applied safely in the operating room within the few minutes available for resuscitation. External electric stimulation of the heart should therefore be tried before resort to thoracotomy and cardiac massage.

*Douglas[25] has also described a case of ventricular standstill that followed intravenous administration of procaine amide (200 mg.) for a cardiac arrhythmia associated with an acute myocardial infarction; external electric stimulation resuscitated the patient promptly.

In addition to the cases described above, we have personally attempted resuscitation with the cardiac pacemaker unsuccessfully in 9 cases in which cardiac arrest developed unexpectedly during jugular puncture, intravenous pyelography, bronchography, cardiac catheterization, endotracheal intubation, hip nailing, cholecystectomy and cardiac surgery. In 2 of these the circulatory arrest was due to ventricular fibrillation, which terminated with cardiac massage or electric countershock applied directly to the heart, but both patients succumbed. In the remaining 7 patients electric stimulation was applied within five to a hundred minutes of the onset of arrest, usually after prolonged, ineffective massage.

These failures emphasize two critical problems of unexpected circulatory arrest: the responsiveness of the heart to stimulation diminishes progressively with continued anoxia; and effective ventricular beats cannot be stimulated by the pacemaker during ventricular fibrillation. The interval between circulatory arrest and the resumption of effective ventricular output must be brief, probably less than three minutes, if cerebral and cardiac function is to return unimpaired. Avoidance of excessive delay depends upon immediate *recognition* of the circulatory arrest and immediate institution of a prearranged *program* for resuscitation.

Recognition of Arrest (Cardiac Monitor)

Cardiac arrest may pass unrecognized in the unconscious, anesthetized patient until irreversible changes have occurred. Disappearance of pulse and blood pressure may not be noticed for minutes during the intervals between routine determinations by the anesthetist. Cessation of arterial and cardiac pulsations, absence of bleeding and cyanosis of the blood may be observed by the surgeon only after excessive delay, particularly when arrest occurs before the incision is made or after it has been closed, as in many cases. There may be considerable delay in the appearance and recognition of other indications of circulatory arrest, such as pupillary dilatation, respiratory arrest and generalized cyanosis.

A practical monitoring device to signal immediately the cessation of the heart beat would obviate crucial delay in recognizing the onset of arrest. Ideally, such an alarm system should be simple and cheap enough to allow its routine application to all patients during anesthesia.

Immediate recognition of cardiac arrest depends on continuous registration of some physiologic activity that can be used as a measure of effective circulation. Such a monitor of circulation may be activated by heart sounds (amplifying stethoscope), by arterial pulsations (amplifying stethoscope, plethysmograph or intra-arterial needle) and by electric activity of the heart (electrocardiogram).

Selection of a technic of monitoring involves consideration of the difficulties with each method. Monitoring the mechanical activities (heart sounds and arterial pulsations) requires delicate positioning of the pick-up device, which may be easily disturbed by minor movements. Such interference may mask the cardiac activity or may produce false alarms. Registration of heart sounds is also unsatisfactory because of their diminished intensity in some patients and frequent interference from extraneous noises. Registration of arterial pulsations alone is insufficient because disappearance of pulsations may result from peripheral vascular collapse as well as from cardiac arrest. In our opinion registration of the electric activity of the heart is the preferable technic. Unexpected cardiac arrest in the operating room is a sudden event in which interruption of electric activity is the initial disturbance.[28] To be sure, electric activity may persist after myocardial contractions and arterial pulses have stopped, but this occurs as a late phenomenon in the severely depressed or dying heart, and circulatory failure will already have been obvious for some time.

Visual registrations of cardiac activity (for example, flashing light and electrocardiographic tracing on paper or oscilloscope) require constant, close human observation if the moment of arrest is to be recognized. This moment of arrest may be missed with intermittent electrocardiographic observations. The person needed to watch and interpret the tracing constantly could more easily monitor the circulation without a machine by feeling the pulse. However, for continuous, prolonged observations such a human monitor is impractical.

Cardiac arrest due to ventricular standstill or ventricular fibrillation can be recognized immediately without the necessity of constant observation of the monitor by means of an *audible* signal of each heart beat. Since cessation of this signal may not be noted promptly, a separate alarm bell should be included to be activated by ventricular standstill. Ventricular fibrillation will also be recognized promptly either by a sounding of the alarm or by an irregular buzz.

The use of such electric instruments in the operating room in the presence of anesthetic gases involves the hazard of explosion. This hazard can be reduced if the instruments are moved away from the explosive gases, elevated 150 cm. (5 feet) from the floor or enclosed in explosion-proof casing.

In summary, we believe that a cardiac monitor should register the electric activity of the ventricles by an audible signal of each heart beat and should also sound an alarm upon the onset of cardiac arrest. In 1 well documented case[29] with such a monitor,* thoracotomy was performed and cardiac massage begun eighteen seconds after the onset of arrest. The routine application of a cardiac monitor to all patients under anesthesia would give greatest assurance of immediate recognition of cardiac arrest. To be sure, the successful cases reported above dem-

*Manufactured by the Electrodyne Company, Norwood, Massachusetts.

onstrate that a program of resuscitation may be successful if it is started promptly, even without a monitor.

Program of Treatment

Once cardiac arrest is recognized, a prearranged program of resuscitation (Table 1) should be instituted at once. The infrequency of this emergency in any one hospital leads to unfamiliarity with the details of a resuscitative program. The limited time available for successful action does not permit any hesitation or fumbling. The program must be organized in detail and rehearsed frequently so that all personnel and equipment are kept in a state of immediate readiness.

In the first minute of this program thoracotomy may be deferred to permit the trial of simpler resuscitative procedures. Even with this deliberate sixty-second delay, if treatment starts immediately upon the onset of arrest, thoracotomy and cardiac massage can still be accomplished well within the three-minute limit for successful resuscitation. Indeed, Lahey[7] described a most successful program with 67 per cent complete recovery in which thoracotomy was delayed for sixty seconds to permit cardiac puncture and intracardiac injection of epinephrine and procaine.

Immediately upon the recognition of arrest the anesthetist or surgeon should call for the electric pacemaker and at the same time confirm the diagnosis of arrest by feeling for a pulse (femoral, carotid, aortic or cardiac) and listening for the heart sounds. Time is so vital after the onset of circulatory arrest that the anesthetist should announce its passage at intervals of ten or fifteen seconds until circulation has been restored.

Since ventricular standstill is the more frequent cause of circulatory arrest, treatment for standstill should be instituted immediately unless the mechanism is known to be fibrillation. Although electrocardiographic identification of the cardiac mechanism is useful, treatment should not be delayed to obtain a tracing, but resuscitative procedures should be applied at once.

While the external pacemaker is being applied, one should attempt to stimulate the heart mechanically by slapping the precordium forcefully or by massaging the heart through the diaphragm when the abdomen is open. Intracardiac needle puncture may also be performed, and epinephrine hydrochloride (0.1 to 0.3 ml. of 1:1000 aqueous solution) may be injected before thoracotomy if an external pacemaker is not immediately available.

If the electric pacemaker is in the operating suite and if the personnel have been drilled in its use, it can be applied within thirty to forty seconds. Ideally, as in several of the successful resuscitations reported above, the electric pacemaker should be attached before anesthesia; then stimulation can be started within a few seconds. The electrodes should be smeared with electrode paste and held firmly with plastic handles 5 to 8 cm. (2 or 3 inches) apart on the precordium. The frequency of stimulation may be set between 60 and 100 per minute. The amplitude of stimulation should be raised quickly to an effective level or as high as possible. Effective stimulation will be recognized immediately by return of arterial pulses; it must then be continued as long as necessary for spontaneous cardiac activity to reappear. Intrinsic, sustained cardiac rhythm usually reappears promptly. If it fails to return within an hour or two, sympathomimetic amines may be administered by intravenous infusion to arouse a spontaneous ventricular rhythm — epinephrine hydrochloride, for example, may be given in gradually increasing amounts beginning with 4 microgm. per minute (15 drops per minute of a solution containing 4 ml. of 1:1000 aqueous epinephrine in 1000 ml. of 5 per cent glucose or 0.85 per cent saline solution).

TABLE 1. *Program of Resuscitation from Unexpected Cardiac Arrest in the Operating Room.*

Ventricular standstill	88%
Ventricular fibrillation	12%

Circulation must be restored within 3 minutes.
Delay in *recognition* or *treatment* of arrest is fatal.
Do not wait for an electrocardiogram.

I. MECHANICAL STIMULATION OF HEART:
- Slap precordium
- Cardiac puncture
- Massage through diaphragm during laparotomy

II. CARDIAC PACEMAKER (if immediately available):
- Effective in ventricular standstill
- Ineffective in ventricular fibrillation or prolonged anoxia

III. OPEN CHEST AND MASSAGE HEART:

For persistent ventricular fibrillation:
1. Electric countershock: 60-cycle a-c, 150 volts, 0.15 second
2. Drugs: procaine, procaine amide, KCl

For persistent ventricular standstill:
1. Cardiac pacemaker applied directly to heart
2. Drugs: epinephrine, calcium gluconate

External electric stimulation of the heart will be ineffective if the mechanism of arrest is ventricular fibrillation or if the heart is unresponsive because of prolonged anoxia or excessive drugs. If the cardiac pacemaker fails to resuscitate the patient within one minute of the moment of arrest, the chest must be opened promptly, and the heart massaged. The efficacy of massage will be recognized immediately by return of arterial pulses and constriction of the pupils; this procedure must then be continued as long as necessary for spontaneous cardiac activity to reappear.

If ventricular fibrillation or ventricular standstill persist for more than a few minutes despite effective massage, measures should be undertaken to restore an effective ventricular rhythm. In the presence of persistent ventricular fibrillation, defibrillation should be attempted by electric shock or by drugs.

Countershock (60-cycle alternating current, 150 volts, 0.15 second) may be applied across large electrodes on each side of the heart and repeated several times at one-minute intervals if necessary. Potassium chloride (10 milliequivalents), procaine hydrochloride (doses increasing from 5 to 15 ml. of 1 per cent solution administered at intervals of a few minutes) or procaine amide (100 mg. repeated at intervals of a few minutes) may be injected into the left atrial or ventricular cavity.

Ventricular standstill may persist despite effective massage, may recur after massage or may follow defibrillation. Electric stimulation may then be applied directly to the heart, preferably by needle electrodes a few millimeters apart. Epinephrine hydrochloride (0.2 ml. of 1:1000 aqueous solution) or calcium gluconate (4 ml. of a 10 per cent aqueous solution) may be injected into a cardiac chamber.

During these resuscitative procedures, artificial respiration with oxygen is always necessary. Other auxiliary measures such as intravenous infusions of blood or other fluids and vasopressor drugs (norepinephrine and epinephrine) may also be necessary to help maintain an adequate blood flow.

After resuscitation, the patient must be under constant observation for two or three days because arrest may recur. In the cases reported above such recurrences were frequent and would have been disastrous if it had not been for the external electric pacemaker. Cardiac activity should be observed continuously for the immediate detection of cessation of circulation. The electric pacemaker should be attached and ready for instant use.

Summary and Conclusions

A method of external electric stimulation has been developed that will arouse the heart from ventricular standstill and will maintain effective, externally paced beats for as long as necessary.

Eight patients with arrest occurring unexpectedly during various diagnostic and therapeutic procedures were resuscitated by the electric pacemaker; thoracotomy with cardiac massage was not required in any of them. Five recovered completely.

A program has been developed for the treatment of unexpected cardiac arrest in the operating room. External electric stimulation of the heart is used as the initial resuscitative measure before resort to thoracotomy and cardiac massage.

Routine application of a cardiac monitor would permit immediate recognition of cardiac arrest and increase the likelihood of complete recovery.

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INHIBITION OF CORTICOSTEROID SECRETION BY AMPHENONE IN A PATIENT WITH ADRENOCORTICAL CARCINOMA*

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AMPHENONE was synthesized in 1950 by Allen and Corwin[1] as one of a series of substituted desoxybenzoins and was selected by Hertz and his collaborators[2,3] as a compound of potential biologic interest because of its structural relation to synthetic estrogens. These investigators found that the substance exerted progestational activity in the rabbit, and a partly progestational, partly estrogenic activity in the rat. In addition, amphenone was shown to produce enlargement of both the adrenal and the thyroid glands. Later studies concerned primarily the nature of the adrenal enlargement and it was suggested that amphenone interfered with the production of active adrenocortical hormones, leading instead to the deposition of large amounts of inactive lipid material in the cells of the zona fasciculata and the zona reticularis of the adrenal cortex. In the hypophysectomized dog the intravenous administration of amphenone led to the abrupt suppression of the secretion of 17-hydroxycorticoids after ACTH administration as measured by the corticoid content of adrenal-vein blood.[3,4] When added in vitro to adrenal slices, amphenone similarly inhibited the production of 17-hydroxycorticoids from suitable precursors.[5] It was shown further that the process interfered with by amphenone is likely to be an ACTH-dependent one since the secondary adrenal enlargement occurred only in the presence of ACTH. Similarly, the goitrogenic activity of the compound was pituitary dependent, whereas its effects on the female genital tract appeared to result from a direct action on the uterus and vagina.

Hertz and his collaborators[6] administered amphenone to patients with extensive metastatic breast cancer to evaluate its effects on adrenal function. They observed an irregular decrease in adrenocortical secretion as measured by the excretion of 17-hydroxycorticoids in the urine, but, with the dosage used, a constant suppression of 17-hydroxycorticoid secretion could not be achieved. The finding of marked adrenocortical hypertrophy at autopsy suggested that the failure to obtain complete suppression might have been due to excessive secondary compensatory secretion of ACTH. When amphenone was administered in large doses to man, a sedative action regularly occurred, and this made higher dosage impracticable.

It seemed reasonable to assume that amphenone administration would be most effective in the presence of adrenocortical tissue not responsive to ACTH stimulation since a compensatory secretion of ACTH in that event would be without effect. Such a situation might be postulated for adrenocortical carcinoma. Furthermore, the extraordinary histologic distortion of adrenocortical cells produced by amphenone suggested that the resulting gross intracellular lipid deposits might interfere with further tissue growth. Thus, when a patient with advanced metastatic adrenocortical carcinoma was admitted to the Peter Bent Brigham Hospital, the evaluation of the effects of amphenone seemed clearly indicated.

METHODS

The urinary levels of 17-hydroxycorticoids were determined by the method of Reddy,[7] and the urinary 17-ketosteroids by a modification of the method of Drekter et al.[8]; urinary glucose excretion was measured according to Froesch and Renold,[9] with the use of glucose oxidase. Plasma levels of free 17-hydroxycorticoids were determined by the technic of Nelson and Samuels,[10] and those of conjugated 17-hydroxycorticoids by that of Reddy et al.[11]

CASE REPORT

S.D. (P.B.B.H. 5H689), a 41-year-old housewife, was admitted to the Peter Bent Brigham Hospital on April 13, 1955, with the diagnosis of Cushing's syndrome due to an adrenocortical carcinoma with metastases. She had been healthy and active until early in 1950, when she suffered partial loss of vision in the right eye. A diagnosis of retrobulbar neuritis due to multiple sclerosis was made at that time. The eyesight gradually improved, and there were no further neurologic disturbances although a slight deepening of the voice was noted — a symptom that did not progress during the next 3 years. During the last 2 years before admission, she noticed progressive hoarseness as well as very gradually increasing growth of hair on the chin, thinning of hair on the scalp and mild acne over the chest. During the last year there had been increased growth of pubic and axillary hair associated with some rounding of the face that became quite marked during the last 3 months. In November, 1954, the patient failed to menstruate (her menstrual history had been normal until that time) and began to gain weight rapidly; she gained 13.6 kg. (30 pounds) during the next 2 months. In December, 1954, she first noted swelling in the left supraclavicular area. During February, 1955, she began to note marked polyuria, poly-

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dipsia and polyphagia. Although her appetite was good, she continued to feel weak, becoming increasingly fatigued, and a small abscess of the thigh developed that was drained surgically and healed. She went to Florida in March, but, feeling unwell, was seen by a physician, who found glycosuria and a fasting blood sugar of 300 mg. per 100 ml.; he suggested that she return to Massachusetts for treatment. She was admitted to her local hospital on April 2, when she was found to have diabetes, hypertension (a blood pressure of 190/100), limitation of diaphragmatic excursions on the left side and a left supraclavicular mass. A biopsy of the mass was carried out, and the histologic appearance was compatible with the diagnosis of carcinoma of the adrenal cortex. She was given NPH insulin, 50 units daily, but was only poorly controlled on this regimen. During the last month before admission, she lost approximately 11.3 kg. (25 pounds) in weight.

The past history was noncontributory, and there was no family history of diabetes, cancer or endocrinopathy.

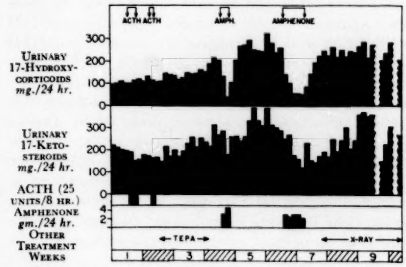

FIGURE 1. *Effect of Amphenone B on Urinary Excretion of Adrenal Steroids in a Forty-one-Year-Old Woman with Metastasizing Adrenocortical Carcinoma.*

Physical examination disclosed a well developed, hoarse, middle-aged woman with a round, plethoric face and prominent eyes. She was perspiring freely. There was an increase of body hair and a decrease of scalp hair, with temporal thinning. There was a buffalo type of obesity, with only mild to moderate muscle wasting. The skin appeared and felt quite thin, although there were no striae. There were petechiae on the lower arms after the blood pressure had been taken. The blood pressure was 180/120. Mild acne was noted over the anterior aspect of the chest and upper quadrants of the abdomen. The thyroid gland was not palpable. There was a large, movable, hard, supraclavicular mass, 5 by 8 by 5 cm. The heart was essentially normal. Examination of the chest disclosed dullness, decreased breath sounds and fremitus at the left base posteriorly with fixation of the left hemidiaphragm. The abdomen was obese, soft and nontender, and there was some fullness in the left flank although no definite mass could be outlined. The liver edge was felt at the right costal margin. The spleen was not palpable. Pelvic examination showed questionable enlargement of the uterus and of the clitoris. Neurologically, the examination was negative.

Laboratory studies on entry showed the urine to be clear with a + test for protein, a ++++ test for sugar and a ++ test for acetone. The hematocrit was 46 per cent, the white blood count 10,000 with 77 per cent neutrophils. Absolute eosinophil count on 2 occasions was 0. The platelets appeared to be normal. Blood urea nitrogen was 9 mg., and the serum protein 5.3 gm. per 100 ml. During the 1st 3 days after admission, the blood glucose values varied from 60 to 200 mg. per 100 ml. despite insulin therapy averaging 65 units a day. The serum bicarbonate was 26 millimols and the serum chloride 100 milliequiv., the sodium 140 milliequiv., the potassium 3.8 milliequiv., and the calcium 5.3 milliequiv. per liter. The serum alkaline phosphatase was 2.8 Bodansky units, and the serum cholesterol 173 mg. per 100 ml. Liver-function studies were within normal limits. A stool was negative for occult blood. Uropepsin levels averaged 7500 units per 24 hours. The basal metabolic rate was +10 per cent. The protein-bound iodine was 1.8 microgm. per 100 ml., and the radioactive-iodine uptake 3 per cent in 24 hours. The plasma volume was 2390 ml., and the red-cell mass 1420 ml. An electroencephalogram was normal.

X-ray examination of the heart and lungs revealed the left leaf of the diaphragm to be paralyzed although there was no definite evidence of pleural effusion. Skull films were normal. X-ray examination of the abdomen, including an intravenous pyelogram, showed displacement of the left kidney by an extrarenal mass in the region of the upper pole. In addition, slight to moderate hydronephrosis was present on the left side. The right kidney appeared normal. No erosion of the bones could be demonstrated, and there was but slight, generalized osteoporosis.

The urinary excretion of 17-hydroxycorticoids and 17-ketosteroids was measured daily and has been charted in Figure 1, together with the major items of the therapeutic regimen. This serves as an over-all illustration of the course during the 9 weeks in the hospital.

It is apparent that grossly abnormal quantities of both 17-hydroxycorticoids and 17-ketosteroids were excreted, the former measuring approximately 100 mg. (normal, 1 to 10 mg.), and the latter approximately 200 mg. per day (normal, 10 to 20 mg.). No increase in the excretion of either 17-hydroxycorticoids or 17-ketosteroids occurred during the intravenous administration of ACTH on 2 occasions, thus confirming the lack of ACTH responsiveness of the steroid-producing tissue. Figure 1 also shows that during the 1st half of the hospital stay a gradual increase in the daily amounts of excreted steroids occurred, a plateau being reached approximately during the 5th week. The abrupt changes in steroid excretion during the 2 periods of amphenone administration are discussed below.

In addition to the 2 courses of amphenone, the therapeutic agents used were thio-tri-ethylene-phosphor-amide (TEPA) and local irradiation. A total of 120 mg. of TEPA was given over a period of 12 days. This did not produce any striking clinical change other than a possible softening of the supraclavicular mass. On the other hand, the maximal dose of TEPA likely to be tolerated was reached since a marked depression of all formed blood elements occurred and persisted for some 2 weeks after the end of the administration of the compound, with subsequent gradual return to normal levels. Local irradiation to the left flank was administered because of increasing pain and without definite evidence of effectiveness.

The clinical course in general was marked by progressive deterioration, by increasing pain in the region of the left costovertebral angle and flank, radiating along the costal margin and to the left shoulder, and by repeated left-sided pleural effusions yielding bloody fluid that contained many tumor cells. In addition, progressive deterioration of the psychologic situation occurred, with episodes of acute anxiety, at times correlated with difficulty in breathing. During the 10th hospital week, a biopsy of the supraclavicular mass was to be performed. On the way to the operating room the patient became acutely dyspneic and cyanotic, and, although an intratracheal tube was inserted immediately and artificial respiration applied, cardiac arrest occurred within 1 hour. At post-mortem examination, the terminal episode was shown to have resulted from massive pulmonary embolism. Further findings included an orange-sized tumor of the left adrenal gland and many lymphatic metastases along the left retroperitoneal and retropleural space, with invasion of the diaphragm and of the left pleura and with further metastatic involvement of the left supraclavicular and axillary lymph nodes. Profuse hematogenous spread, with many hepatic and bony metastases, had occurred. The contralateral adrenal gland was atrophic. The pituitary gland was grossly normal.

Results of Amphenone Administration

Amphenone B was administered in two courses. The first course lasted for two days. An initial dose

of 1.0 gm. was given by mouth, followed by 500 mg. every three hours throughout the first day. On the second day, the dose was increased to 500 mg. every two hours. As shown in Figure 2, the urinary 17-hydroxycorticoids were measured in each six-hour portion of urine, and a great decrease in their excretion was apparent from the twelfth hour onward. Throughout the second day the rate of 17-hydroxycorticoid excretion was less than a fifth of that on the control day. After discontinuation of the drug, the pretreatment level was reached within twenty-four hours. A further dramatic change during amphenone therapy concerned the severity of the glycosuria and the insulin requirement. Urinary glucose excretion dropped from approximately 40 gm. daily to somewhat over 20 gm. on the first and to 2.5 gm. on the second day of amphenone administration, with an immediate increase to pretreatment levels after discontinuation of the drug. The changes in blood glucose levels concurred. The significance of these glucose changes was enhanced by the simultaneous decrease in the dose of insulin administered, the total daily dose dropping from 74 units on the day before treatment to 13 units on the first day and to 0 on the second day of amphenone therapy. Insulin was also withheld during the first day after treatment. It should be added that food intake during the first day of amphenone therapy was not essentially different from that during the days before therapy but that some anorexia was present on the second day. As previously demonstrated in Figure 1, the changes in the urinary excretion of 17-ketosteroids were much less striking than those previously described for the 17-hydroxycorticoids.

Whereas no significant side effects of the therapy were noted during the first day of amphenone administration, moderate anorexia set in during the second day and was followed by subjective feelings of anguish and agitation. Toward the end of the second day, the patient became acutely uncomfortable, complaining of profuse sweating, prostration and depression. On physical examination, she was found to be cool and clammy, with evidence of peripheral vasoconstriction, and her blood pressure was 120 systolic, 80 diastolic, as compared with a previous level of 180 systolic, 110 diastolic. Administration of the drug was discontinued, and gradual improvement was seen during the next twelve hours. Although a direct toxic effect of amphenone could not be excluded, this episode was interpreted in retrospect as being suggestive of the syndrome observed after acute steroid withdrawal.

From this first trial of amphenone it was concluded that a considerable effect on the adrenal secretion of 17-hydroxycorticoids had been obtained, as evidenced not only by the decreased urinary steroid excretion but also by the spectacular improvement of the disturbance in carbohydrate metabolism. It was believed, however, that a more gradual reduction in the steroid secretion would be preferable, and that it might be necessary to supplement the too rapidly decreasing endogenous steroid production by the administration of decreasing doses of exogenous hormone.

Throughout the second course of amphenone therapy, which lasted for five days, 250 mg. of the compound was administered by mouth every two hours during the day and 500 mg. every four hours during the night. Although a more gradual fall in

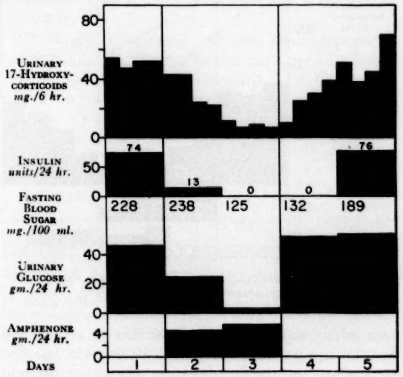

FIGURE 2. *Immediate Effect of Amphenone B on the Urinary Excretion of 17-Hydroxycorticoids and on Insulin Requirement in a Patient with Adrenal Carcinoma.*

urinary 17-hydroxycorticoid excretion was achieved, the patient began to complain of weakness and sweating from the third day onward, and it was considered advisable to administer 8 mg. of fluorohydrocortisone (approximately equivalent to 160 mg. of cortisone) on the third day and 4 to 6 mg. on the following days. On the fifth day of amphenone administration, and despite the concurrent administration of fluorohydrocortisone, she again complained of profuse sweating, prostration and abdominal distention; her skin was cool and clammy, and the blood pressure dropped to 100 systolic, 60 diastolic. In addition, she went through an episode of psychotic behavior with somatic hallucinations and acute anxiety, the latter sufficiently severe to indicate the intravenous administration of amobarbital sodium (Amytal) for relief. At that time the serum potassium was 3.3 milliequiv. and the serum sodium 126 milliequiv. per liter. X-ray examination of the abdomen showed a distended, air-filled stomach. Amphenone administration was discontinued, a Levin tube was inserted, and the intravenous infusion of 40 milliequiv. of potassium chloride in 1 liter of saline solution was started; rapid improvement ensued. Fluorohydrocortisone was continued for three days after discontinuation of amphenone therapy.

Again, the effects of amphenone on the urinary excretion of 17-hydroxycorticoids were striking (Fig. 3), the twenty-four-hour excretion dropping from 260 mg. to an average of 50 mg. per day during the last three days of therapy. Plasma 17-hydroxycorticoid levels showed a remarkable drop of both the free and the conjugated fractions during the period of amphenone administration. It should further be pointed out that the urinary excretion of 17-hydroxycorticoids rose from 50 mg. on the last day of amphenone treatment to 197 mg. on the third day after discontinuation of therapy even though the patient was at that time maintained on 6 mg. of fluorohydrocortisone daily. This adds further evidence for the lack of dependence on ACTH of the steroid-producing tissue, since 6 mg. of fluorohydrocortisone daily is sufficient to suppress 17-hydroxycorticoid secretion by the normal adrenal glands.[12,13]

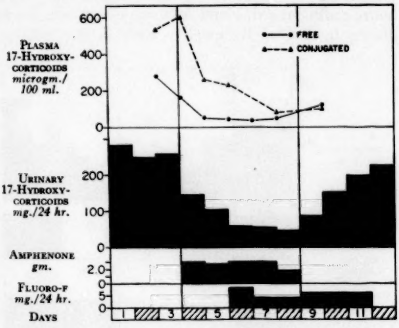

FIGURE 3. *17-Hydroxycorticoids in Urine and Plasma during Amphenone B Therapy.*

An attempt was made to keep the patient on a constant dietary regimen throughout this second period of amphenone administration. Although a truly constant regimen could not be maintained, the results of the metabolic studies performed (Fig. 4) demonstrated that marked sodium retention was present throughout and that the urinary excretion of potassium decreased during amphenone therapy with a rebound after withdrawal of the drug and hence on the day when adrenal secretion of glucocorticoids returned. The urinary excretion of glucose, nitrogen and phosphate similarly decreased during amphenone therapy and despite the concurrent administration of fluorohydrocortisone.

In addition to the studies mentioned, the following parameters were checked every second day before, during and after amphenone administration: hematocrit, leukocytes, thrombocytes, serum protein, cholesterol, calcium, phosphate, bilirubin, thymol turbidity and endogenous creatinine clearance. No significant changes could be detected. Adequate studies of changes in thyroid function could not be made since values for protein-bound iodine and I^{131} uptake were vitiated by the recent administration of iodine-containing dye.

Discussion

From the studies that have been presented it appears that the secretion of adrenal corticoids by a metastasizing adrenocortical carcinoma was markedly inhibited by the oral administration of amphenone B in amounts of 3 to 5 gm. daily in divided doses. This conclusion seems justified since it is based on measurements of both urinary and plasma 17-hydroxycorticoids as well as on changes in the metabolic effects of the secreted hormone. The urinary metabolites of amphenone do not interfere with the colorimetric methods employed. A clear-cut action of amphenone in man has thus been established, at least for adrenocortical tissue lacking its normal dependence on ACTH. This lack of ACTH dependence was inferred from the absence of any demonstrable response on the part of the tumor tissue when stimulated with intravenously administered ACTH, as well as from the rapid increase in corticoid excretion after

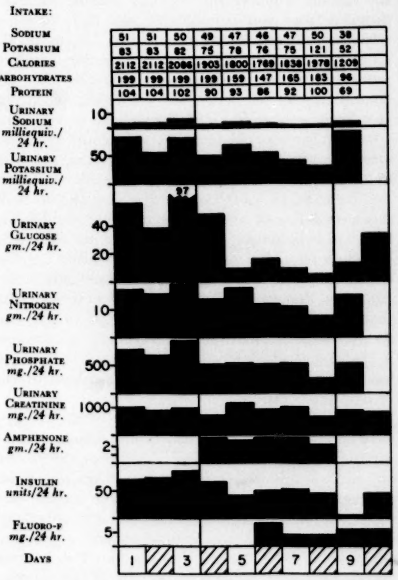

FIGURE 4. *Metabolic Studies during Amphenone B Therapy. The daily intake of sodium (milliequivalents), potassium (milliequivalents), calories, carbohydrates (grams) and proteins (grams) is indicated at the top of the figure.*

amphenone withdrawal even though ACTH-suppressing doses of fluorohydrocortisone were being administered at that time.

Whereas the effects of amphenone on the adrenal secretion of carbohydrate-active steroids were profound and immediate, as measured both by the changes in 17-hydroxycorticoid levels in blood and urine and by the alteration in the severity of the diabetes, the effects on the urinary excretion of 17-ketosteroids were relatively slow and unimpressive. Indeed, the changes in 17-ketosteroid excretion that did occur could well have represented mainly a decreased catabolism of 17-hydroxycorticoids to 17-ketosteroids. More recent findings, however, have shown that amphenone metabolites in the urine may interfere with the Zimmerman color reaction used for the determination of urinary 17-ketosteroids. When chromatographic technics were employed definite suppression of 17-ketosteroid excretion during the period of amphenone B administration became apparent.

Toxic effects of amphenone on bone marrow, red blood cells, liver or kidney were looked for, but none were found. Twice, however, when striking depression of steroid secretion was achieved, a syndrome developed that included sweating, prostration, hypotension and anorexia. This clinical picture appeared classic for acute adrenocortical insufficiency as seen in patients maintained on high-steroid doses after abrupt cessation of the hormone therapy. It is further of interest that during the second of these episodes severe hyponatremia occurred despite continued marked positive sodium balance, a finding highly suggestive of a sudden rearrangement of total body sodium distribution. This observation is in agreement with the normal sodium value found in a patient with previously undiagnosed Addison's disease admitted to a hospital in classic and severe crisis.[14]

The duration of amphenone administration was too short to permit even a preliminary evaluation of the possible effect of the drug on tumor growth.

Summary and Conclusions

A case of Cushing's syndrome due to a metastasizing carcinoma of the adrenal cortex secreting large amounts of adrenocortical steroids is presented. The tumor tissue lacked the responsiveness to ACTH stimulation characteristic of normal adrenocortical tissue. The administration of amphenone B to this patient resulted in a decreased secretion of carbohydrate-active corticoids, as evidenced by the changes in the levels of 17-hydroxycorticoids in plasma and in urine as well as in the biologic effects of these steroid hormones.

The available evidence indicates that amphenone B specifically interferes with the synthesis in adrenocortical tissue of biologically active 17-hydroxycorticoids from inactive precursors. A similar interference with the synthesis of potentially androgenic 17-ketosteroids has not yet been demonstrated.

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ANTERIOR DISPLACEMENT OF THE DESCENDING DUODENUM AS AN AID IN THE DIAGNOSIS OF RETROPERITONEAL TUMOR*

A Roentgenographic Sign of Possible Significance in Some Cases of Enlargement of the Right Adrenal Gland

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LAWRENCE AND BOSTON, MASSACHUSETTS

THE roentgenographic demonstration of an adrenal tumor depends on the visualization of a soft-tissue mass above the kidney as seen on a plain film of the abdomen.[1] One then hopes to demonstrate caudal displacement of the kidney with some alteration of its normal axis as seen on an intravenous or retrograde pyelogram. A laminagraph may be of some help in localizing an adrenal tumor. At times, however, all these technics fail to demonstrate a tumor satisfactorily, and one is forced to resort to more complicated methods of x-ray investigation. Perinephric air insufflation, as practiced by Cahill,[2] has been effective in demonstrating adrenal enlargements that escape detection by simple x-ray studies. Although many large series of air injections have been reported without complication, there have been some case reports of fatal air embolism, and the possibility of this accident has made some clinicians cautious in advising this diagnostic procedure and others unwilling to advocate its use.

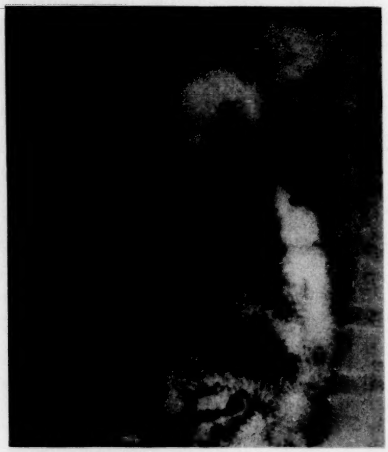

FIGURE 1. *Gastrointestinal Series in April, 1951.*

More recently, Ruiz-Rivas[3] has advocated presacral injection of oxygen to obtain an adequate retroperitoneal pneumogram. This technic has the advantage of demonstrating both sides of the retroperitoneal space and of showing the renal and adrenal areas bilaterally after a single injection. Even with this technic, however, gas embolism is a possibility, and subcutaneous emphysema and abdominal discomfort often follow the injection. Furthermore, at times, confusing shadows, difficult of interpretation, are obtained, and one often ends up the diagnostic study by recommending bilateral surgical exploration.

Translumbar aortography[4] has been utilized as a means of obtaining further information by visualization of the blood supply to the adrenal and renal areas, but this procedure has also been followed by serious and, occasionally, even fatal reactions.[5]

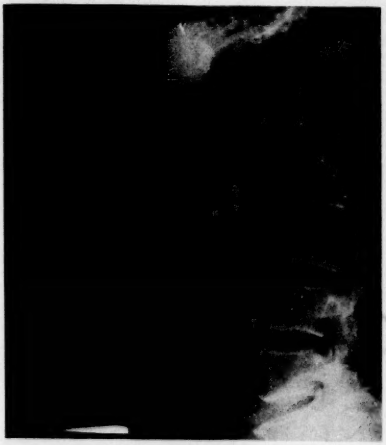

FIGURE 2. *Gastrointestinal Series in August, 1951.*

Recently, Hamm and Scordamaglia[6] commented on the difficulty of interpreting soft-tissue shadows in the area of the left adrenal gland and recommended gaseous distention of the stomach as a means of eliminating troublesome shadows produced by the fundus of the stomach in the roentgenographic deline-

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ation of the enlargement. Tumors of the left adrenal gland have been shown to displace the stomach forward and medially, and at times this roentgenographic sign has helped demonstrate such a tumor.[7]

Our purpose in submitting the case reported below is to call attention to the anatomic relations between the right adrenal gland and the second, or descending, portion of the duodenum. We wish further to remark on the relation of the second portion of the duodenum to the lumbar spine as seen in the view in the right lateral recumbent position after oral ingestion of barium. These observations suggest the possibility that anterior displacement of the descending duodenum as a sign of right-sided adrenal enlargement has enough significance to warrant the recommendation that an upper gastrointestinal series, with a view of the stomach and duodenum in the right lateral recumbent position, be taken in any patient in whom the diagnosis of right adrenal pathology is being entertained. The ease and safety with which this examination may be done seem to recommend its use before recourse is had to more complicated x-ray technics, such as translumbar aortography and retroperitoneal pneumography. Perhaps the procedure can follow pyelography in the order of performance of the various roentgenographic studies.

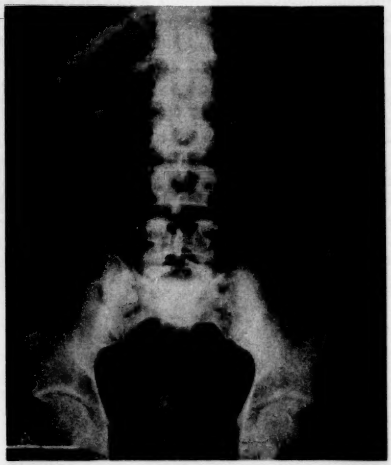

FIGURE 3. *Intravenous Pyelogram in August, 1951.*

In the case reported below, this sign was present in three consecutive upper gastrointestinal series, and yet the intravenous pyelogram and retrograde pyelogram failed to show any significant caudal displacement of the right kidney or alteration of its normal axis. At both operations, the second portion of the duodenum was seen to be displaced anteriorly by the adrenal tumor.

FIGURE 4. *Retrograde Pyelogram in November, 1951.*

CASE REPORT

A 50-year-old factory worker was seen in March, 1950, complaining of pain in the right upper portion of the abdomen and right lower anterior aspect of the chest of 1 year's duration.

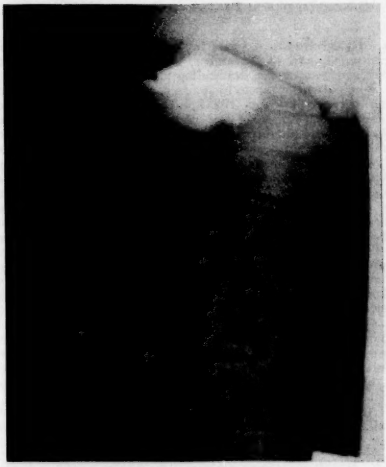

FIGURE 5. *Roentgenogram Taken in the Right Lateral Decubitus Position in October, 1951.*

Physical examination was completely negative. No mass could be felt in the abdomen or loins, and no local tenderness elicited. There were no endocrine abnormalities. The blood pressure was 140/70.

Urinalysis, blood counts, an electrocardiogram and films of the chest were within normal limits. An upper gastrointestinal series showed a prepyloric peptic ulcer.

The patient was placed on an antiulcer medical regimen, which resulted in the healing of his ulcer as determined by

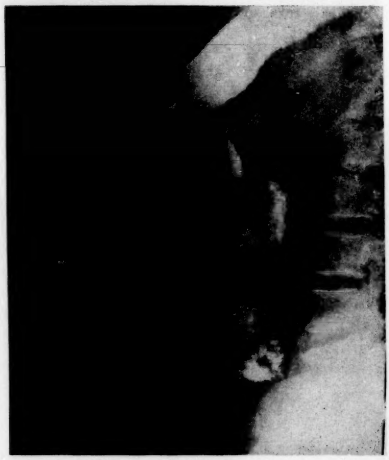

FIGURE 6. *Roentgenogram Taken in the Right Lateral Recumbent Position in February, 1952.*

a 2d gastrointestinal series in June. Nevertheless, the pain continued, and in November, a 3d series showed anterior displacement of the descending duodenum.

The patient began to have fever, the temperature fluctuating between 98 and 102°F. The possibility of a retroperitoneal lymphoma was considered, and a lymphoma dose of x-ray therapy was given through the back. Gastrointestinal series repeated in April (Fig. 1), and August, 1951 (Fig. 2), showed further anterior displacement of the duodenum. An intravenous pyelogram in August (Fig. 3), was not considered remarkable, and a retrograde pyelogram in November (Fig. 4) did not appear abnormal. In further x-ray examinations of the upper gastrointestinal tract in the right lateral decubitus position made in October (Fig. 5) the anterior displacement of the descending duodenum could also be demonstrated. In February, 1952, a repeat view of the duodenum in the right lateral recumbent position showed a further increase in the anterior displacement of the descending duodenum (Fig. 6).

On February 29 a transperitoneal exploration was carried out. A retroperitoneal tumor displacing the duodenum anteriorly was found. It lay anterosuperior to the upper pole of the right kidney and was considered nonresectable. A biopsy was obtained, and the wound closed. The pathological report was carcinoma of the adrenal cortex.

Another attempt at surgical removal by a thoracoabdominal approach was made on March 10, and a large tumor of the right adrenal gland was removed intact without undue difficulty, owing to the excellent exposure allowed by this incision. Here, again, at operation, one could see the marked degree to which the descending duodenum was displaced anteriorly.

The patient became completely asymptomatic for the 1st time in 5 years. He remained so for 2 more years, but recurrent pain and x-ray evidence of pulmonary metastases have developed and he is rapidly failing from carcinomatosis.

DISCUSSION

Anatomically, the base of the right adrenal gland is in contact with the medial and anterior aspects of the upper pole of the right kidney. The anterior surface of the gland is covered by peritoneum, with the exception of a small area near the lower end, which is covered by the extraperitoneal surface of the duodenum, to which it is connected by loose areolar tissue.

The second portion of the duodenum is 7 to 10 cm. long and extends along the right side of the vertebral column as far down as the upper border of the fourth lumbar vertebra. It is fixed definitely in position by fusion of its lateral visceral peritoneum

FIGURE 7. *Roentgenogram Taken in the Right Lateral Recumbent Position after the Oral Ingestion of Barium.*

to the parietal peritoneum of the lateral abdominal wall and is closely attached to the median surface of the kidney by a strong peritoneal fold, the duodenorenal ligament.[8,9] A film of the stomach and duodenum taken in the right lateral recumbent position after the oral ingestion of barium shows the normal relation between the descending duodenum and the vertebral column (Fig. 7).

Scheinmel and Mednick[10] have attempted to establish average normal retrogastric measurements in the right lateral recumbent and left lateral upright positions after oral ingestion of barium for persons of varying habitus—namely, the hyposthenic, sthenic and hypersthenic. These authors emphasize the value of these measurements and of the left and right lateral recumbent positions in disclosing space-

occupying lesions in the high and middle epigastric and right and left lateral paravertebral regions at the same levels. Variations from the normal measurements were utilized to detect space-occupying retroperitoneal tumefactions in the upper abdomen.[11] None of the 8 cases presented, however, were adrenal tumors.

The level of apposition of the duodenum with the anterior aspect of the adrenal gland and kidney may vary in different persons. In some cases, in which the retroperitoneal duodenum anatomically is in relation with the kidney at a lower level, the right adrenal gland would probably not produce significant displacement of the duodenum. But in cases in which the duodenum has a higher level of apposition with the adrenal base,[12] one may reasonably expect to demonstrate this sign. Furthermore, Cahill,[13] in justifying his preference for the oblique subcostal transperitoneal surgical approach, has observed that the direction of growth of an adrenal tumor is "downwards and anterior"—and therefore well calculated to cause anterior displacement of the descending duodenum.

In clinical practice, adrenal tumors are not frequently encountered — hence, the present solitary case report. We hope that others encountering tumors of the right adrenal gland may have occasion to test the possible value of this roentgenographic sign.

Conclusions

Anterior displacement of the descending duodenum as visualized by a view of the upper gastrointestinal tract in the right lateral recumbent position after the ingestion of barium appeared to be significant as a roentgenographic sign of enlargement of the right adrenal gland in an instance in which there was no obvious caudal displacement of the kidney.

The anatomic relations between the right adrenal gland, descending duodenum and lumbar spine appear to give a satisfactory explanation for this roentgenographic observation.

This is a simple and safe x-ray examination that may perhaps render unnecessary more complicated diagnostic tests such as lumbar aortography and retroperitoneal pneumography in an occasional patient with a tumor of the right adrenal gland.

We are indebted to Dr. Fletcher H. Colby, of the Massachusetts General Hospital, for helpful criticism.

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MALIGNANT ARGENTAFFINOMA ASSOCIATED WITH CARDIOVASCULAR ABNORMALITIES

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DETROIT, MICHIGAN

THERE has recently been considerable interest in the association of argentaffin tumors with valvular lesions of the heart.[1-5] The unusual character of this association was first recognized by Biorck, Axen and Thorson,[1] although they were able to find a few cases previously reported. In general these patients all had argentaffin tumors, which had often extensively metastasized to the liver. However, in a case reported by Arnett and Long[6] the tumor was thought to be a carcinoma of the pancreas, and in 1 of the cases of Rosenbaum et al.,[7] the neoplasm was interpreted as a bile-duct carcinoma. The cardiac component of the syndrome has ordinarily consisted of stenosis of the pulmonary valve, but the tricuspid valve has also been involved frequently.[2] In addition, many of these patients have exhibited unusual vasomotor disturbances characterized by facial cyanosis and telangiectasis[8]; in some cases this feature has made clinical diagnosis of the syndrome possible. With the description of isolation of chemical agents such as 5-hydroxytryptamine from carcinoid tumors[9] speculation has arisen that there may be a causal relation between the existence of such neoplasms and the development of the cardiovascular phenomena. Recent work by Sjoerdsma, Weissbach and Udenfriend[10] describing a simple test for a serotonin

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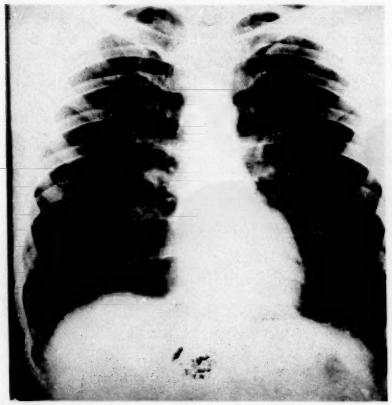
metabolite (5-hydroxyindoleacetic acid) found in the urine offers an additional diagnostic tool.

A case of this type in which roentgenologic changes were of considerable help in suggesting the diagnosis is presented below. In addition, morphologic studies in previously reported material have not been recorded in detail despite the fact that such data may help evaluate the character of the cardiac lesion.



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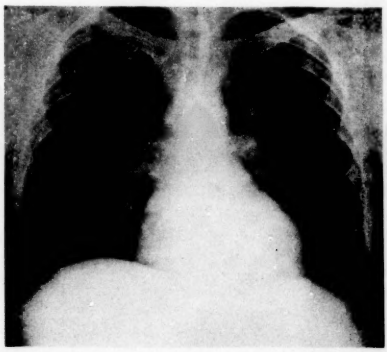

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FIGURE 1. *Roentgenograms, Showing the Right-Sided Heart Enlargement between 1948* (A) *and 1954* (B).

CASE REPORT

L.W. (H.F.H. 536997), a 45-year-old rural mail carrier, was first seen in 1948 complaining of cramping abdominal pain after eating that was worse after eating of fatty foods. He stated that this pain had been intermittently present over the preceding 15 years. He usually avoided fatty foods because of the pain that might result. Most of the attacks of pain lasted 2 to 4 days and were not accompanied by vomiting or jaundice. Occasionally, he had noted pale stools. During the year before his 1st visit, he had had 1 to 4 stools a day; sometimes the stools were liquid. Over the past six years his weight had dropped from 68 kg. (150 pounds) to 59.9 kg. (132 pounds).

The past and family histories were noncontributory.

Physical examination showed some telangiectasis of the face. The heart sounds were normal, and the rhythm regular at a rate of 84. The aortic 2d sound was greater than the pulmonic. The blood pressure was 130/80. Examination of the abdomen was within normal limits, as were proctoscopy and biliary drainage.

At this time the patient had x-ray studies consisting of a barium-enema examination, upper gastrointestinal series, a film of the chest and gall bladder examination, all of which showed nothing remarkable.

Examination of the blood disclosed a red-cell count of 4,640,000, with a hemoglobin of 13.4 gm. per 100 ml., and a white-cell count of 6700.

He was treated with belladonna, phenobarbital, vitamins and a laxative. During the same year he was subsequently treated for hemorrhoids and for chronic prostatitis.

Two years later (1950) he was seen because the attacks of abdominal pain persisted, becoming worse during the 4 months before his visit, and also because of nocturia and urinary frequency. Again, general physical examination produced no significant positive findings, and, in particular, no cardiac murmurs were recorded.

In 1951 the patient was seen first because of rectal bleeding, thought most likely to be due to hemorrhoids, and subsequently because of vomiting followed by 3 days of abdominal cramps. Again, auscultation of the heart was negative. In spite of therapy, abdominal cramps continued and hyperactive peristalsis was heard. He was admitted to the hospital, where plain films showed dilated loops of distal small bowel filled with gas. A barium enema gave no evidence of obstruction in the large intestine. A small-bowel study demonstrated an obstruction in the distal ileum. At an exploratory operation a carcinoid tumor of the distal ileum was found. The tumor could not be removed, but an enteroenterostomy was done. At that time there was already spread to the regional lymph nodes, peritoneum and liver. Other tests during this admission, including studies of stool, blood, urine, nonprotein nitrogen and liver function were all within normal limits.

After operation the patient was seen because of diarrhea, but this gradually subsided. Four months later the liver was enlarged, and 10 months after operation it was extremely large and nodular. The liver edge was palpable 15 cm. below the right costal margin.

TABLE 1. *Data from Cardiac Catheterization.*

LOCATION	PRESSURE			OXYGEN‡	OXYGEN SATURATION
	SYSTOLIC	DIASTOLIC	MEAN		
	mm. Hg.	*mm. Hg.*	*mm. Hg.*	*vol. per cent*	*%*
Middle of rt. atrium*	30/5		15	9.2	39
Rt. ventricle	35/5		18	8.1	34
Pulmonary artery, rt.†	9/0		5	—	—
"Wedge" (rt.)	—		4	—	—

*Pressure tracing shows "ventricularization" indicative of marked tricuspid insufficiency (note that systolic pressure almost at ventricular level).

†Pressure curve indicates valvular type of stenosis.

‡Oxygen capacity, 23.7 vol. per cent.

He was not seen again until 1954, 30 months after operation, when he reported in response to a follow-up letter. At that time the liver edge was palpable 10 cm. below the xiphoid, and for the first time note was made of a gross systolic murmur, of Grade 3 to 4, best heard over the tricuspid area. An increase in the telangiectasis of the cheeks and nose was also observed.

Chest films and fluoroscopy at this time showed a considerable increase in the size of the heart that was due to enlargement of the right atrium and ventricle (Fig. 1).

Six months later ankle edema was observed; the murmur was again heard, and the question of pericardial friction rub was raised. Shortly thereafter, he returned because of dyspnea, lassitude, swelling of the ankles, marked flushing and cyanosis of the head and chest, and some distention of the neck and arm veins. At that time there was an aortic systolic murmur, of Grade 1, and a harsh Grade 3 to 4 systolic murmur in the left 4th interspace along the

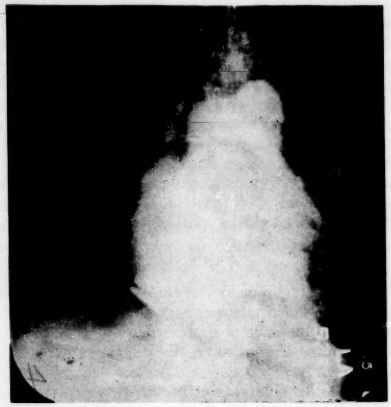

FIGURE 2. *Angiocardiogram, Confirming Right-Sided Enlargement and Demonstrating Stenosis of the Pulmonary Valve, with a Small Main Pulmonary Artery.*

sternal border with a short diastolic component. Tricuspid insufficiency was considered.

An electrocardiogram showed a rate of 85, with a PR interval of 0.14 and a QRS complex of 0.08 second, with the patient vertical. There was sinus rhythm, with tall P waves in Leads 2 and 3. Hypertrophy of the right ventricle was shown in the unipolar extremity and precordial leads.

He was treated by restriction of salt, Diamox and Thiomerin. On this regimen dyspnea and ankle edema cleared in about 1 week.

He was seen again 6 months later (1955), when the peculiar cyanosis of the face and hands was noted. This was particularly marked over the malar prominences. There was slight distention of the neck veins and some ankle edema.

It was thought that, because of his color and slight fullness of neck and arm veins there might be a metastasis to the mediastinum and for this reason cardiac catheterization was done. This showed an increase in the pressure in the right ventricle, with a drop between the right ventricle and pulmonary artery (Table 1). The catheter was withdrawn to the superior vena cava; 70 per cent Urokon was injected, and an angiocardiogram obtained.

The angiocardiogram showed enlargement of the right atrium and right ventricle, with persistent filling of the right atrium. There was a well demonstrated stenosis at the pulmonary valve, with a relatively hypoplastic main pulmonary artery (Fig. 2).

From that time on the patient failed steadily, and on the theory that some of the valvular disturbances might be the result of metastatic carcinoid tumor to the heart, he was given 4 x-ray treatments of 300 r, measured in air, for a total of 1200 r, with the use of a 10-x-10-cm. portal,

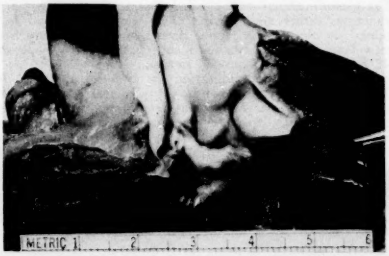

FIGURE 3. *Appearance of the Pulmonary Valve. Two leaflets are visible and show marked thickening and shortening, with some obliteration of the commissure. Note the discrete appearance of the lesion.*

directed at the cardiac-valve area. He continued to fail and died.

Post-mortem examination showed marked emaciation. There were severe marked congestion and lividity of the face and neck. The abdomen was distended. The peritoneal surfaces were greatly thickened and numerous adhesions were present. There were numerous masses of gray-white

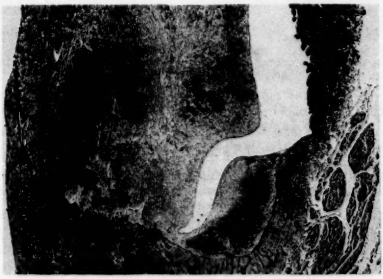

FIGURE 4. *Low-Power View (Weigert's Elastic-Tissue Stain) of the Base of the Pulmonary Leaflet. The superficial character of the endocardial fibrosis is clearly demarcated by the internal elastic membrane. The valve structure itself (on the left) is essentially unchanged.*

tumor in the mesentery of the bowel binding the loops together.

The heart weighed 280 gm. There were a few subepicardial hemorrhages. The right atrium was considerably dilated. The pulmonary valve was stenotic, and the cusps thickened, with fusion of commissures (Fig. 3). The orifice was 4 cm. in circumference. The other valves appeared normal; the aortic valve measured 10 cm., the mitral valve 9 cm., and the tricuspid valve 12 cm. The myocardium was normal in appearance except for right-sided hypertrophy, the wall of the left ventricle being 1.5 cm. and that of the right 1 cm. thick. There was a diffuse, moderate

increase in thickness of the endocardial lining in the right atrium.

The liver weighed 2800 gm. and was studded with tumor nodules ranging from 10 cm. to 1 cm. in diameter. The larger nodules frequently showed central necrosis. The adrenal glands were embedded in gray-white tumor tissue, but not actually invaded. Both kidneys were grossly pitted with scars; each weighed 170 gm. No tumor was present. The gastrointestinal tract showed considerable autolysis and numerous tumor nodules, but these were serosal and had caused no ulceration. Tumor masses in the mesentery had caused considerable angulation and fixation of bowel loops. All other structures appeared normal.

On microscopical examination the essential alteration in the heart appeared to consist of a marked endocardial thickening. This was somewhat loosely textured and was composed of spindle-shaped fibroblasts in a stroma, which seemed edematous. Special stains showed little collagen and no elastic tissue. The process involved the inner aspect and the base of the pulmonic leaflets (Fig. 4) and the entire endocardium of the right atrium (Fig. 5). The lesion was sharply demarcated from underlying areas by the internal elastic membrane. Occasionally, small vascular channels were encountered at the junction of the thickened

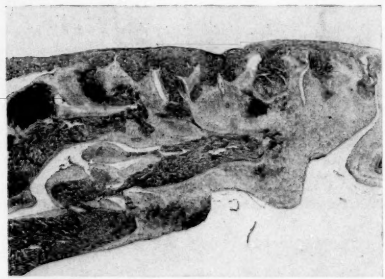

FIGURE 5. *Marked Uniform Endocardial Fibrosis Lining the Right Atrium (Weigert's Elastic-Tissue Stain). There is no elastic-tissue component.*

endocardium and the underlying tissues. Around some of these in the valve were found collections of lymphocytes and plasma cells. There was no evidence of lesions of the Aschoff-body type. The most remarkable feature of the sclerosis was its bland appearance and superficial character. There was also a curious focal thickening of the intima in one of the coronary veins, suggesting changes similar to those encountered in the endocardium. The epicardium showed a mild chronic inflammation together with serous atrophy of the fat.

The argentaffin tumor was quite typical in appearance and was scattered through the liver. A few small nodules were also encountered in the myocardium, as well as a microscopic focus in the posterior pituitary gland. The liver substance showed marked fatty metamorphosis. A few smaller arteries in the lungs demonstrated some increased intimal thickening, but in general no abnormalities were found in vessels anywhere else.

DISCUSSION

The presence of a widespread carcinoid tumor in the abdomen was established when laparotomy was performed because of intestinal obstruction. In the future, however, this diagnosis will be suspected in patients who present facial telangiectasia and cyanosis, particularly when these findings increase during a period of observation.

Physical examination and radiologic examination of the heart were both conclusive in establishing the point that the cardiac abnormality was acquired during the period of observation. There was nothing to suggest any intercurrent disease, such as rheumatic fever, which could have been responsible. An angiocardiogram and cardiac catheterization both indicated pulmonary stenosis of the valvular type.

There seems to be little doubt that the mediator of the effect of the carcinoid on the heart is serotonin or its metabolites. This process is similar to fetal endocardial fibroelastosis[11] in that both lesions show the primary changes restricted to the endocardium, with an increase in thickness, and in both the process can involve valves, with the production of stenosis. No etiologic agent is yet apparent for fibroelastosis. Fibroelastosis most commonly involves the left side of the heart whereas no left-sided lesions have been reported in association with malignant argentaffinoma. This lesion also differs from fibroelastosis in that there is no evidence of incorporation of elastic tissue in the plaques. In fibroelastosis as described by Craig[12] the entire architecture of the valve is involved with fibrous thickening and hyalinization whereas, in the case reported above, the valve was distorted by endocardial change only.

SUMMARY

A case of malignant argentaffin tumor with an increase in facial telangiectasia and cyanosis, as well as the development of the murmurs of tricuspid insufficiency and pulmonic stenosis during observation, is presented.

Progressive enlargement of the right atrium and ventricle was shown by x-ray study and fluoroscopy. Angiocardiography confirmed the diagnosis of pulmonary stenosis of the valvular type.

Cardiac catheterization excluded a shunt and indicated the valvular lesion.

Microscopical study showed connective-tissue thickening of the endocardium of the right atrium and of the pulmonary valve with stenosis of the valve.

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SPECIAL ARTICLE

PAIN AND THE INDIVIDUAL*

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IF modern man suddenly had to give up any of his hard-won and cherished gains over the forces of nature during the past century and a half, I suggest that the one he would part with most reluctantly, even with fear or abject terror, is the art of relieving pain by anesthesia. He has become so accustomed to the thousands of daily miracles of relief of pain during surgical operations and other similar procedures that he takes them for granted — at least those outside the specialty of anesthesiology do. Furthermore, increasingly complicated miracles are expected, and it is assumed anesthesiologists are on the road to solving all the knotty problems of relief of pain. Sober reflection reveals, however, that there is still a long way to go.

CONCEPT OF PAIN

Pain is one of the oldest burdens of mankind. From the moment of birth to the final end of all sensation that comes with death it is either present or looming large as a threat. It almost literally lies in wait for the child who does not judge his environment carefully and accurately. It afflicts him from the inside when he ingests food unwisely or when some accident of growth produces a disarrangement of tissues or organs. It affects him — apparently from the outside, to his primitive way of thinking — when he encounters a sharp object, a hot substance or a fall to the ground, when he has a fight with his playmate, or when he has incurred enough displeasure of his parents to result in corrective measures. As he becomes an adult a whole succession of painful experiences await him, and every move he makes may bring acute discomfort. The line between pain and pleasure he finds hard to maintain. Pain may be literal in terms of acute physical discomfort, or it may be symbolic in terms of bereavement, anxiety, apprehension or fear. There can be no sharp dividing line because each reinforces or may produce the other. Anxiety may, and frequently does, cause physical illness resulting in pain, and all pain produces fear and anxiety to some degree, depending upon the degree of sensitivity in the make-up of the sufferer.

If pain is so prevalent and a potential threat behind every movement he makes, why has man not made a supreme gesture of ridding himself of all suffering by self-destruction or, at the very least, why has he not given in to fear or depression? Possibly one answer is that pain is a prime necessity of existence. The patient who has suffered some cerebrovascular accident resulting in loss of sensation to a portion of the body, the one who has had a spinal-cord disease or injury cutting pain-sensation tracts and the leper, with his cutaneous anesthesia, all testify in part to the great difficulty that would exist in merely perpetuating life except for the great protective value of pain and the capacity to experience pain. Here is another of life's many paradoxes: pain is at one and the same time one of man's greatest enemies and his necessary friend.

Yet no one really likes pain.

Some pain, or some degrees of it, are actually enjoyable. Most organized athletics entail a varying degree of it. Fatigue can be painful and yet pleasurable, too, if an end can be seen to it. Sexual activity may be painful in a way that is highly acceptable, and pain may become erotic in certain unusual situations. The martyr may welcome the pain of persecution if his belief in the righteousness of his cause is overpowering.

The pain of a counterirritant may seem to deaden the original inciting discomfort. The pleasure in having had pain in the past and having escaped from it is frequently great indeed, and may form the chief ingredient in reminiscences of those who have lived lives of high adventure. The great majority of the satisfactions that human beings enjoy derive in some measure from the relief of tension. If it were not for hunger, food would not be so enjoyable. If one were never lonely, friends would not be so welcome, nor would friends be so welcome if one knew that they would stay with one always. Warmth is a welcome relief from cold. And so the contrasts can be extended indefinitely. Similarly, the absence of pain, or even good health, cannot be

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appreciated and enjoyed so much by those who have never experienced pain or ill health as by those who have.

Pain that is completely harmless may be borne easily — the kind that one experiences in opening a jar with a tight lid, or in a test of strength of any kind. Filling a tooth, having an injection, removal of a foreign body or opening an abscess may be intensely painful but is usually readily borne by most people unless there have been earlier conditioning experiences of a harmful nature. The most severe pain is that of unknown origin or of an ominous nature.

The attitude of people toward pain differs greatly, both within one individual and between different persons. It is well known to everyone that strong attention to an outside source raises the threshold of pain to a considerable degree. A headache may disappear when one is busy with the need for communicating with other persons in a pleasurable setting, only to recur when one again becomes quiet and is alone. Similarly, a headache may appear when one has a disagreeable task or experience in prospect. If one is already in an irritable state from a number of unacceptable events in one's life, the threshold for pain is lowered. Previous pain seems to decrease tolerance for further suffering. A severely depressed patient does not consider pain a deterrent to his desire to end his life, and the hysterical patient at times suppresses the capacity for feeling pain entirely.

Pain is also more easily borne when hope is high, when the end can be seen, when the reason for it is clear and when there is complete confidence in the skill and competence of the physician. Religious contemplation is often successful in altering pain or at least in minimizing the outer reactions to such discomfort.

Some people may unconsciously use pain as a means of testing the affection of other people. For such persons pain is always a symptom of illness, for which they are not responsible, entitling them to an increased amount of love and kindness. When pain is present, they may be superficially more comfortable than at other times. From that point it is not a long step to the use of pain, again by unconscious mechanisms, as a means of manipulating other members of the family or friends.

Organic and Psychogenic Pain

Along these lines Penman[1] recently discussed "Pain as an Old Friend." He had studied 275 patients with *tic douloureux* who had been treated surgically for relief of long-continued pain. He found that whereas nearly all of them were glad to lose the pain, many had vexation from the paresthesias that resulted from the operation. In some the actual loss of pain brought unhappiness. He divided them into five groups depending upon their response to treatment. In the first, constituting about 23 per cent of the total number, the patients were unreservedly glad. In the second, 55 per cent, they were glad despite some distress. In the third, 2 per cent, there were severe neurotic symptoms soon after treatment. In the fourth, with 10 per cent of the total, milder neurotic symptoms developed after a considerable interval. Constant misery was the lot of the members of the fifth group, making up the last 10 per cent of the patients.

Penman comments that if pain is present for a long time it may become the sufferer's chief occupation, a stimulus to bravery, a refuge from an intolerable situation (that is, an alternative to a neurosis), grist to the emotional mill of professional sympathizers or a habit that engenders a cluster of other habits.

On one occasion I observed a patient, who had finally worked out a satisfactory method of preventing her migraine headaches, who said with real concern, "But what will I do without this pain?" She then went on to say that it had been very useful to her in avoiding social and other situations in which she did not feel adequate.

Those who work mainly in the field of psychiatry have often noted how the relief of psychogenic pain without relief of the underlying psychologic conflicts or tensions may precipitate a depression or some other manifestation of severe internal conflict. Likewise, the alternation of hypomanic behavior and some type of psychosomatic illness such as duodenal ulcer is common in psychiatric practice. Treatment of a disagreeable symptom without adequate consideration of the deeper reasons behind it often tends to make the overt discomfort worse, the patient finding it necessary to cling to the symptom as his chief defense with greater and greater tenacity. If he senses that the physician really doubts the existence of the pain, which usually means either that he does not understand its etiology or has a bit of inward contempt for psychogenic pain, the patient is likely to hold on to it almost with desperation. In a sense the unconscious mechanisms of defense combat the physician by overvaluing the pain and holding on to the symptom to prove him wrong and the patient right. The fact that placebos occasionally relieve pain is a cause for optimism concerning the possibility of ultimately learning how to relieve such pain by more open and lasting means. Placebos occupy a place in the relief of apparently physical pain somewhat analogous to the use of hypnosis in the removal of a symptom in a patient who has hysteria. As a research instrument each has its uses; as a means of treatment both are subject to misuse and may become the source of real harm.

Although the relief of pain and suffering has always been a chief aim of the physician, a systematic consideration of its place in the total personality config-

uration has never been accomplished in a satisfactory manner. As Szasz[2] has pointed out, it is the custom in medical and psychiatric writing to attach the terms "organic" and "psychogenic" to pain to define its meaning. Such a distinction refers to the judgment of the observer rather than to the pain experience and indicates that the pain must be located in some particular place. Szasz indicates the close analogy of the relation between "objective" fear and "neurotic" anxiety and that between "organic pain" and "psychogenic pain." In objective fear the sources of danger can be seen, and the appropriate response attempted. In neurotic anxiety the source of the danger cannot be easily ascertained, and hence an observer may judge it "not dangerous." Similarly, an observer may readily delineate the causes of organic pain and take appropriate measures for its relief, but psychogenic pain is much more difficult for the observer to understand, and, since he cannot readily see its sources, he may consider it insignificant.[2]

A patient is somewhat like a child in that his capacity for communicating with the person on whom he is most dependent — the physician in one instance, and the parent in the other — is concerned fully as much with attitudes and mannerisms as it is with the literal meaning of the words used. Thus, the physician who unconsciously as well as consciously places a higher valuation on organic pain than on psychogenic pain effectively says to his patient by this unspoken means of communication, "If your pain is organic or 'real' I am very much interested in you and will do everything I can to help you. If your pain is 'psychogenic' or 'imaginary' then I am not so concerned, I do not know what to do, so I will do anything I can to divert you from my area of responsibility." In this way the patient who already suffers from pain and the added anxiety of having its source unidentified has new sources of anxiety.

Individual Interpretation

This suggests that a central concept for the physician to keep in mind when dealing with his patient suffering from any of the many varieties of pain is what it means to the patient. Obviously, it means different things to each one, depending on what the patient's idea of his body image and personality may be. The suffering physician, minister, banker, farmer, child or mentally retarded person all have different fantasies about the meaning of their discomfort. In some cases the patient may be troubled more by what he thinks he may have than by what he actually does have if the two happen to be different. The least variation in action, manner or speech on the part of the physician from what the patient conceives to be a straightforward approach to his problem adds to his suffering. Lack of knowledge on the part of the physician he can tolerate with relative ease, because he knows that all knowledge is to some extent incomplete. Lack of candor he cannot endure without ill results.

Relief of Pain

Pain constricts mental functioning just as strong emotion does. In the absence of such discomfort the mind wanders back and forth over the whole range of conscious awareness, the horizon being limited only by the person's own intellectual thought processes and his range of experiences, actual or vicarious. As pain becomes more and more severe, a patient can only devote his attention to the portion of his body or his personality that is apparently affected. He speculates on its meaning, its threat to him, whether it is permanent or temporary, whether it can be eased or not, or whether it indicates he will lose a portion of his body or his life. Memory and concentration are thus grossly impaired. Increasing pain is psychologically more devastating than decreasing pain. When all hope of life is gone and pain is overwhelming, the most severe tests of character occur. Some patients bear it stoically, calling on the deeper resources of confidence and faith; others become frantic and either try to end their lives or get someone to achieve this goal for them. At this point the physician also is beset by the most difficult pressures he is ever called upon to withstand. Fletcher[3] has concisely expressed the logical contradiction posed by the Hippocratic Oath:

> The contradiction is there because the oath promises two things: first, to relieve suffering, and second, to prolong and protect life. When the patient is in the grip of an agonizing and fatal disease, these two promises are incompatible. Two duties come into conflict. To prolong life is to violate the promise to relieve pain. To relieve the pain is to violate the promise to prolong and protect life.

Fletcher, a noted and respected theologian, comes to a conclusion on the subject of euthanasia with which I cannot agree. "Medicine contributes too much to the moral stature of men to persist indefinitely in denying the ultimate claims of its own supreme virtue and ethical inspiration, mercy."[4]

This ideal physician, which all try to be in some measure, will never inflict pain needlessly or thoughtlessly, nor will he relieve it by means that will be advantageous for the moment but productive of increased complications later on. The placebo given partly out of irritation, partly out of revenge, the needless surgical operation done at the patient's strong insistence ("he might otherwise have a less skillful surgeon do it" is the usual rationalization), the unwise reassurance and failure to consider all the patient's needs so far as that is possible — all these detract from the fullest benefit to be derived from the physician-patient relation.

The mark of the true physician is his sensitivity to the needs and suffering of others. Perhaps compassion is the word best fitted to express the feel-

ing of a physician for his suffering patient, but this does not mean that the physician can lose his objectivity while being sympathetic with his patient. Neither does it mean that his defense against his own anxiety and concern for the patient should take the form of cynicism, or a coldly scientific, hard-bitten exterior manner.

"Reverence for Life"

Albert Schweitzer,[5] in *Memoirs of Childhood and Youth,* gives an exquisite description of the development of this particular quality. As a child Schweitzer was sickly and unimpressive. As he began to grow strong his sensitive imagination developed rapidly. Very early in his memories was the episode of his being stung by a bee, which caused him to cry loudly and made him the center of much family attention. Soon he noted that he was getting much satisfaction from his crying even though the pain had stopped. He went on for a while and then became miserable because of his guilt feelings over the exaggeration. When he went to school he could not endure wearing warmer or better clothes than his fellows. On first hearing brass instruments playing, he almost fainted from excess of pleasure. He could not stand hunting and killing birds or other wild animals unnecessarily. Finally, he hit a neighbor's dog in the eye with a whip, causing excruciatingly severe corneal pain that made the dog roll in the snow, writhing in agony. He could not get the cries of the dog out of his mind for weeks. It was of such experiences as these that the theory of reverence for life was born and developed. And it is from such experiences that the physician develops the artistic sensitivity to the needs and sufferings of others that ennobles his character and heightens his pleasures as well.

Discussion

I have considered some aspects of the way pain and the individual interact with one another. The other combinations are practically limitless. What I hope I have said is that the role of the physician in the relief of pain consists of far more than knowing the physiology and the pharmacology of pain and using this knowledge in an optimum manner, however important and basic that may be. The physician may make his greatest contribution to the relief of pain when he combines his necessary scientific knowledge with a never-ceasing attempt to attain and then increase his sensitive awareness of suffering in the patient and in addition a high degree of respect for him. When this combination has been sincerely attained, the troubled patient senses it as surely as a child senses sincerity and integrity in his parents, and the physician has indeed become a source of great comfort.

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MEDICAL PROGRESS

APNEA AND RESPIRATORY DISTRESS IN THE NEWBORN INFANT*

Physiologic Background, Resuscitation and Supportive Technics

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APNEA and later respiratory distress of unknown etiology are the two types of respiratory problems that are most important in the newborn period. Their physiologic background is the subject of the first part of this review. Technics of resuscitation in cases of apnea, supportive therapy in the respiratory-distress syndrome and, where possible, the prevention of both are considered in the second and third sections. Although the details of the clinical, roentgenologic and pathological aspects of respiratory problems in the newborn and their differential diagnosis will be presented in a subsequent review, a summary of the principal etiologic possibilities is given in Table 1. A specific diagnosis, particularly when specific therapy is possible, is obviously necessary for proper management of both apnea and later respiratory distress.

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The first group includes not only infants with apnea but also those whose breathing ceases after a few ineffectual gasps. It seems reasonable to consider these infants in the apneic group and to believe that the immediate cause of the difficulty, like that in pure apnea, is failure of the respiratory center.

The other group includes infants (much more common than the apneic, in our experience) whose respiration begins fairly promptly but is, or soon becomes, labored and inadequate. The rapid and usually regular rhythm indicates that central mechanisms are functioning, but the grunting, the usual presence of retraction and the frequent development of cyanosis as the condition progresses indicate disturbances in the peripheral respiratory apparatus. No one term satisfactorily identifies the probable underlying pathology or the clinical picture, which, when not so severe as to cause death, usually spontaneously regresses between the third and sixth to the tenth day of life. For want of a better designation that used in a paper from this laboratory, "respiratory distress," is employed here.[1] This condition has also been called congestive pulmonary failure,[2] resorption atelectasis or the hyaline-membrane syndrome although the "membranes" have not been found in all the infants who have died and, even when they are present, their significance in the living is not established.

Some newborn infants with respiratory difficulty present a combination of both initial apnea and subsequent respiratory distress. The appraisal of the presently unexplored interrelation of these two types of respiratory problems will be difficult but would be useful in an understanding of the etiology of such distress.

Before the specific devices and technics proposed for resuscitation and support of respiration are discussed, the available physiologic knowledge on which their use should be based is briefly considered, as follows: normal onset and control of breathing; pulmonary function in the normal newborn infant; and alterations of pulmonary function in respiratory distress.

Normal Onset and Control of Breathing

It seems probable that human and other mammalian fetuses make rhythmic respiratory movements in utero,[3,4] and it is certain that a neuromuscular mechanism for starting and continuing such movements is present at least as early as the twentieth week of human fetal life.[5] There is no agreement, and little information, about the constancy of these movements during subsequent intra-uterine life; in some mammals they seem to be kept under an increasing degree of inhibition as term approaches.[3]

The nature of the stimulus initiating extra-uterine respiratory movements is not as yet established. There may well be different stimuli for different infants. It has been proposed that the unimpaired fetus makes respiratory movements as one of several muscular responses to the numerous and sudden sensory stimuli of extra-uterine existence. Under abnormal circumstances, this simple and immediate response may be blocked by the effects of anoxia, trauma or drugs on the infant's central nervous system. A delayed onset of irregular and gasping breathing may then begin when the gas or hydrogen-ion concentrations of the infant's blood are sufficiently altered to stimulate the centers chemically. The broad concept of a usual physical and an emergency chemical mechanism, either of which may initiate breathing, is in accord with many investigations of animals and observations of human deliveries.[3] Whether or not this concept proves correct, it seems unlikely that a single and universal stimulus initiates respiration in every infant who begins to breathe spontaneously. Certainly, the magnitude of the stimulus necessary to cause an effective respiratory response varies greatly.

Table 1. *Principal Types of Respiratory Failure in Newborn Infants.*

Central-Nervous-System Failure (Apnea - Hypopnea)*	Peripheral Respiratory Difficulty
Narcosis	Respiratory distress (congestive pulmonary failure, hyaline-membrane syndrome, resorption atelectasis)*
Prenatal or paranatal anoxia	Aspiration of meconium-containing amniotic fluid
Intracranial hemorrhage or trauma	Pneumonia
Central-nervous-system anomalies & others	Congenital anomalies & others

*Discussion of respiratory failure & its treatment limited essentially to these groups.

In view of the scarcity of definitive data on either the type or the magnitude of stimuli necessary to initiate respiration in the human infant under varying conditions, it is not surprising that some writers believe that the resuscitating physician should assume the dynamic role of inflating the lungs for the baby, whereas others recommend the more passive one of providing an open airway and the proper gas mixture to supplement the infant's own efforts. Should the aim be to take over the infant's breathing or merely to assist him to resuscitate himself? An interesting answer is given by Higgins,[6] who argues that no form of resuscitation is needed for any infant capable of normal survival. Nothing more is recommended than leaving the nonbreathing infant on its side with the body head-downward, 15° from the horizontal. Higgins's results in nearly 2000 deliveries should be consulted by anyone attempting to evaluate more radical procedures.

Any such conservative routine involves some degree of reliance on the special resistance of fetal and neonatal mammals to oxygen lack. This property, as well as the anaerobic metabolism on which it may in part be based, has recently been reviewed by Villee and Kimmelstiel,[7] who have added data on intermediate metabolism to those of Himwich and Faze-

kas,[8] Himwich[9] and Reardon and her co-workers.[10] Villee and Kimmelstiel agree that newborn animals are unusually resistant to oxygen lack, but their data do not indicate the underlying mechanism to be the incomplete breakdown of glucose by any presently understood metabolic pathway. It appears that the presence and degree of anaerobic metabolism cannot be quantitatively estimated from the production of lactic or pyruvic acid in the newborn mammal, and that it is probably not possible to increase or prolong anaerobic metabolism simply by providing extra glucose to the apneic or distressed newborn infant.

No exact statement is available concerning the period of anoxic existence that might be sustained without harm to the human fetus or infant. Brinkman[11] has said that "after 20-40 minutes anoxic changes would be irreversible in the cortex," but this was put forward with several qualifications. Actually, it is impractical and unwise to attempt to set a safe time limit to apnea in the newborn infant because of the variables introduced by the maturity of the infant, the adequacy of cerebral circulation and, especially, the unknown factor of intra-uterine anoxia that may have occurred before or during birth. Experience indicates that in the full-term infant normally delivered after a completely normal pregnancy the onset of respiration may be delayed five or even ten minutes without risk. Neurologic abnormalities acquired during the paranatal period are almost invariably associated with other complicating factors such as bleeding during pregnancy, operative delivery and intra-uterine distress.[12,13]

However promptly respiration may begin after birth, the infant's blood is always relatively low in oxygen at the moment of the first breath. The oxygen saturation of the blood in the umbilical vein when breathing begins averages about 50 per cent,[5] and is rarely above 75 per cent. This suggests that hypoxia could cause the infant's first respiration, a possibility supported by the data of Graham and Wilson,[14] and suggested by them as having a better claim than any other chemical stimulus. In the mammalian fetus the effect of experimentally induced hypoxia appears to be one of delayed gasping and struggling.[3] The effect of experimental reduction of atmospheric oxygen upon the established respiration of the newborn infant is not completely understood. In infants studied by Miller and Smull[15] within twenty-four hours of birth, the tidal and minute volumes of breathing were steadily reduced when 12 or 10 per cent oxygen was given, with no momentary increase suggesting a chemoreceptor response. But in infants of two to seven days, Cross and Warner[16a] and Cross and Oppé[16b] demonstrated that the first result of substituting 15 per cent oxygen for air was a prompt increase in rate and volume of breathing. This apparent stimulation of the medulla through the chemoreceptors was evidently short-lived; as the low-oxygen mixture was continued, minute volumes declined to levels slightly below those preceding its administration. Apparently, the ultimate effect of anoxia is to depress the newborn infant's respiratory center, although this depression may be preceded by a brief interval of chemoreceptor drive. In any event, profound anoxia probably never stimulates breathing. The role of moderate anoxia in the control of respiration by chemoreceptor mechanisms in the newborn infant needs further investigation.

According to Graham and Wilson[14] the carbon dioxide tension in capillary blood of the infant within an hour or less of birth is approximately 35 mm. of mercury and varies between 22 and 47 mm. Tensions above 40 mm., which stimulate respiration in the adult, were rarely encountered; moreover, Graham and Wilson found that in samples taken four to twenty-four hours after birth, the carbon dioxide tended to be still lower than during the first hour. Seemingly, hypercapnea was not driving the normal breathing of these infants; indeed, their breathing might be expected to have been suppressed by these relatively low blood carbon dioxide tensions unless homeostatic mechanisms respond at lower levels of carbon dioxide in the infant than in the adult. On the other hand, blood in the umbilical vein of normal infants before or at the first breath has been reported by other workers[17,18] to have higher carbon dioxide tensions, averaging approximately 40 to 50 mm. of mercury, with a wide range. When respiration is long delayed (as after traumatic delivery) and the clinical picture is that of severe asphyxia neonatorum, the tension in the umbilical vein has been shown by Eastman[19] to be elevated, to an average of 61 mm. in 6 infants, 3 of whom did not survive.

Carbon dioxide does not stimulate intra-uterine respiratory movements of mammalian fetuses when experimentally administered to the maternal animal.[20] But it has repeatedly been demonstrated that carbon dioxide increases the established respiration of either normal full-term or premature newborn infants,[21-23] and this stimulation occurs even when carbon dioxide is added to air in concentration of only 0.5 per cent.[22] Miller[23] has shown that 5 per cent carbon dioxide in air or oxygen increases the tidal volume and minute volume of infants less than twenty-four hours of age by more than 130 per cent. In infants whose respiration has been reduced by five minutes' administration of 12 per cent oxygen the addition of 5 per cent carbon dioxide produced a greater increase in minute volume than a change to air or 100 per cent oxygen. However, because the respiratory-center depression was due to anoxia, the response to 5 per cent carbon dioxide was much further increased when this gas was coupled with air or 95 per cent oxygen instead of the 12 per cent oxygen. Thus, the breathing of infants in reasonably responsive states is stimulated by carbon dioxide, but this does not imply that a similar response is elicited in states of severe depression from anoxia, trauma or other situations in which

carbon dioxide is already elevated. Additional carbon dioxide would presumably act as a cause of further depression.

From what has been said above, it is obvious that the exact types of initial respiratory stimuli and their relative importance have not been established. But since, within an hour of its onset, respiration normally produces a blood oxygen tension only slightly below adult levels, any method of resuscitation or artificial respiration should logically aim at similar levels of blood oxygen and carbon dioxide.

The question of whether an infant's breathing can ever be depressed by administration of too much oxygen or removal of too much carbon dioxide through artificial ventilation remains. Cross and Oppé have shown that established respiration of newborn infants is immediately and slightly reduced when extra oxygen is given[16a,16b] — a response in keeping with an active chemoreceptor mechanism. Since this effect lasts only one or two minutes, it may have escaped the notice of other workers. The more lasting effect of increased atmospheric oxygen appears to be a moderate increase in respiration, not only in infants whose blood is relatively normally oxygenated and whose lungs are apparently normal[16,24] but also in those with respiratory distress.[1] Increased oxygen concentrations also tend to produce regular breathing in the normal premature infants who exhibit periodic respiration in air.[24] The underlying mechanisms by which increased atmospheric oxygen produces these changes are not known. The literature contains no accounts of clinically significant suppression of respiration after the provision of extra oxygen in the newborn period.

Pulmonary Physiology

In addition to the central factors in the initiation, maintenance and control of respiration, peripheral factors are important in relation to initial respiration, continued ventilation and abnormal pulmonary function. As in the description of respiratory-center control, some of the available information is based on animal studies and in vitro experiments, and some on direct observations in newborn infants. It will be apparent from the following discussion that much remains to be learned both about normal and abnormal neonatal pulmonary physiology.

Initial Respirations

For initial expansion of a normal infant's lungs essentially two types of forces must be overcome: surface tension within the air passages and the elastic resistance of the lungs themselves. Other factors, such as the elastic behavior of the thoracic cage and diaphragm, the resistance to the flow of gas within the airways, the viscous (nonelastic) resistance of the lung tissue itself and the inertia of the lung and the thoracic cage, contribute an unknown but probably less important proportion of the total resistance to initial expansion. Gruenwald[25] has shown that when saline solution is used to expand fetal lungs, resistance due to surface tension is relatively insignificant; when air is used surface-tension factors are important. Thus, although amniotic fluid may be inspired into the lungs with relative ease during fetal life, the initial breath of air may require a negative pressure of as much as 15 to 20 cm. of water to exceed surface-tension forces alone. The elastic resistance that must be overcome with the initial respiration of the infant is at present

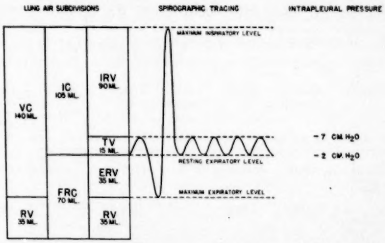

FIGURE 1. *Lung Volumes and Intrathoracic Pressures in a Normal 2.5-Kg. Infant.*

Values have been measured for tidal volume (TV),[27] functional residual capacity (FRC)[28] and crying vital capacity (VC).[29] The partition of vital capacity (VC) into expiratory reserve volume (ERV) and inspiratory reserve volume (IRV) represents extrapolation from adult data,[30] as does the resting expiratory value for intrapleural pressure. Intrapleural pressure changes have been measured in infants as intraesophageal pressure changes.[27]

unknown. Total negative pressures of −40 cm. of water for the first breath of a newborn infant have been reported,[26] and probably half of this is exerted against elastic resistance and half against surface tension. If this partition of pressure is correct, it appears that the lung is considerably less compliant before expansion than after. In any event, the initial respiration of the normal newborn infant probably requires intrathoracic negative pressures four to eight times greater than those needed for later maintenance of respiration (Fig. 1 and Table 2).

In this connection one wonders about the adequacy of the thoracic cage under certain conditions. Measurements indicate that the maximum negative pressures in premature infants are far greater (up to 25 cm. of water)[31] than necessary for maintenance of normal ventilation, but perhaps are inadequate for initial expansion in all cases, particularly if there are abnormalities within the lungs themselves. Measurements of terminal bronchioles[32] suggest that, although not proportionately smaller, their diameter is related to the size of the infant. Since resistance due to surface tension is inversely proportional to the radius of the airway, the smallest infants may require the largest opening pressures for lung expansion. Work by Behrle, Gibson and Miller[33] suggests that this re-

lation exists in the excised lungs of infants examined post mortem. Aspiration of normal amniotic fluid may have a function in expanding the lung and thereby decreasing surface tension and increasing lung compliance — that is, conditioning the lung for expansion.

The initial expansion of the lung at birth has usually been considered to be a function of the thoracic cage. It has recently been suggested, on the basis of a few in vitro observations, that the sudden increase in pulmonary-artery pressure that has been shown to occur in fetal sheep[34] and presumably also occurs in the human fetus with occlusion of the umbilical vessels may produce engorgement and erection of alveolar capillaries and augment expansion of the lungs.[35]

Continued Ventilation

Several characteristic features of respiration of newborn infants should be noted. In the first place they tend to be obligatory nose breathers and have considerable difficulty in adjustment to mouth breathing when this is necessitated by nasal obstruction. Secondly, in infants (as in adults) the principal muscle of respiration during quiet breathing is the diaphragm; the contribution of the thoracic cage is relatively insignificant, and sometimes its movement is paradoxical.[36] In addition the respiratory rhythm of newborn infants is often irregular and, particularly in premature infants, periodic.

Measurements and estimations of various aspects of newborn infants' respiration are shown in Figure 1, and the information is summarized in Table 2. When the values are related on the basis of weight, functional dead space (or the volume of each respiration filling nonfunctioning respiratory passages) is comparable to that of the adult, and the functional residual capacity (Fig. 1) is relatively reduced.[27] A possible teleologic explanation for the high respiratory rates (and small tidal volumes) in infants emerges from measurements of the pulmonary work of respiration. These measurements indicate that the theoretical minimum work of respiration calculated from the available data occurs at the observed tidal volumes and rates[31]; to accomplish the same effective ventilation at adult rates of respiration, the respiratory work would have to be greatly increased.

The application of data concerning the respiratory physiology of newborn infants to the emergency clinical use of resuscitation or artificial-respiration devices is often impractical. However, a knowledge of such physiologic measurements should aid in the intelligent use of the various technics and appears essential for a critical evaluation of methods of initiating or aiding respiration. For example, if positive pressures are used for resuscitation, a knowledge of lung compliance (volume response of the lung per unit of pressure applied) is useful. In the normal infant's lungs, compliance is approximately 5 ml. per cm. of water pressure and is greatly reduced in infants with respiratory distress.[31] Again, induced tidal volumes equal to or less than the functional dead space would be useless for gas exchange. The maximum spontaneous or natural negative pressures (approximately 40 to 60 cm. of water) and their duration (approximately 0.04 to 0.1 second) are also of importance since these figures provide some indication of positive pressures that may be tolerated during resuscitation. Recently, Day et al.[37] have particularly emphasized the importance of the duration of the force applied to the lungs and the direct relation between the duration of the pressure and the disruption of lung tissue.

TABLE 2. *Comparison of Respiratory Parameters in Normal Newborn Infants and in Those with Respiratory Distress.*

SUBJECT	MINUTE VOLUME	RATE	TIDAL VOLUME	VITAL CAPACITY*	ALVEOLAR VENTILATION	ARTERIAL CARBON DIOXIDE TENSION	FUNCTIONAL DEAD SPACE	FUNCTIONAL RESIDUAL CAPACITY	NEGATIVE-PRESSURE CHANGE DURING QUIET RESPIRATION	MAXIMUM NEGATIVE-PRESSURE CHANGE DURING RESPIRATION	LUNG COMPLIANCE	PULMONARY WORK PER MINUTE
Normal 2.5-kg. infant	498 ml.	34/min.	15 ml.	140 ml.	355 ml./min.	32 mm. Hg	5 ml.	70 ml.	5 cm. H_2O	50 cm. H_2O	5 ml./cm. H_2O	1450 gm. cm.
Infant with respiratory distress†	+75%	+90%	−8%	−50%	−30%	+30%	+70%	−45%	+300-500%	±	−80%	+400%

*"Crying" vital capacity.
†Average changes with respiratory distress.

Abnormal Pulmonary Function

It has not yet been explained just how the abnormalities of respiratory function and the morphologic changes that may accompany them are produced by such varied factors as prematurity, maternal diabetes, placental separation, operative delivery and the other obstetric situations in which they commonly occur. In the experience of this clinic, however, progressive respiratory distress not only is much more frequent but also causes far more neonatal deaths than failure of neurologic impulses to start respiration.

One may only speculate on the basic causes of the progressive respiratory distress frequently seen in the newborn period. Increases in surface tension, abnormal cardiovascular-pulmonary relations and

thoracic-cage insufficiencies alone or in combination, may produce or contribute to the final clinical and pathological picture. Recently, a number of authors[38,39] have suggested that neonatal respiratory distress may be related to cardiovascular factors, and Gitlin and Craig[40] have shown that the "hyaline-membrane" material frequently found at post-mortem examination in the alveolar ducts of these infants with respiratory difficulty is probably a fibrin-containing transudate. If the sudden increase in pulmonary-artery pressure that must follow closure of the umbilical vessels were not quickly relieved by expansion of the lungs and concomitant expansion of the pulmonary vascular bed, such a transudation of fluid might occur.

Whatever the etiologic factors are, the observed pathophysiologic consequences of the resulting respiratory distress are shown by the descriptive data of Table 2. It can be seen that some of the important changes are related to an increase in physiologic dead space — that is, the proportion of each respiration wasted in nonfunctioning air passages is increased. Abnormalities of distribution of gas in the lungs, disturbances in gas diffusion across the respiratory epithelium, or vascular changes within the lungs may one or all be the basis of the increase in the physiologic dead space. But whatever the cause, the change necessitates an increase in minute volume to maintain alveolar ventilation. This adjustment is accomplished primarily by an increase in respiratory rate; presumably, the marked reduction in compliance (1 or 2 ml. per cm. of water pressure compared to 5 ml. for the normal infant) makes it impossible for these infants to increase their tidal volume significantly. That the compensatory mechanisms may not maintain adequate ventilation is indicated by the cyanosis and evidence of increased blood carbon dioxide tension often observed even in infants who subsequently survive.

As a result of increased rate and decreased lung compliance the necessary ventilatory adjustments are only made at the expense of very great respiratory efforts, and pulmonary work of respiration is increased to 200 to 400 per cent above the normal level. Although this increased work may be relatively insignificant compared to the entire body metabolism (normal respiration accounts for only approximately 1 per cent of the basal metabolic rate)[27] it may lead to exhaustion of the respiratory muscles themselves and to further anoxia, hypercapnia and death.

Berglund and Karlberg[28] have described in neonatal respiratory distress a reduction by roughly 40 to 50 per cent in the functional residual capacity; this is presumably related to the decreased compliance of the lungs. The relatively small lung volume may be accompanied by a decrease in the volume of pulmonary blood vessels and a secondary pulmonary-artery hypertension. If this supposition is correct it would perhaps account for the cardiac enlargement[41] and prolonged patency of the ductus arteriosus reported in these infants.[42]

(To be continued)

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MEDICAL INTELLIGENCE

SYMMETRICAL PERIPHERAL GANGRENE IN MYOCARDIAL INFARCTION

Report of a Case

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NEW HAVEN AND BRIDGEPORT, CONNECTICUT

SYMMETRICAL peripheral gangrene is not a commonplace event, and yet the initiating factors may vary considerably. Frequently, it complicates severe cases of frostbite, ergotism and ball-valve thrombus with mitral stenosis. It is rarely secondary to congenital cardiac defect,[1] pneumonia,[2] myocardial infarction,[3-5] paroxysmal ventricular tachycardia[6] and severe congestive heart failure.[7] The present case is one of acute myocardial infarction followed by symmetrical peripheral gangrene.

CASE REPORT

A 58-year-old housewife entered the hospital complaining of severe substernal pain radiating to both axillas. The pain, sudden in onset, initially was felt the preceding night while she was in bed. It had persisted unabated until the time of admission.

The past history indicated that in the previous 4 years she had been treated for hypertension and episodes of angina and dyspnea on exertion.

Physical examination revealed a moderately obese, well developed woman who was dyspneic. She did not appear to be gravely ill, and spoke easily and readily. There was no cyanosis, peripheral edema or engorgement of neck veins. A few moist rales were heard at both lung bases posteriorly, but were more extensive on the right. The heart was not clinically enlarged, and there was no palpable precordial impulse. The rhythm was regular. There was a Grade 2 systolic murmur, heard best at the apex. The liver was not palpable. Peripheral pulses were recorded as being present.

The temperature was 98.4°F., the pulse 100, and the respirations 30. The blood pressure was 150/80.

Examination of the urine showed a specific gravity of 1.020, a negative test for sugar and a trace of albumin, with 1 or 2 red and white cells per high-power field. The Venereal Disease Research Laboratory slide was negative. Examination of the blood revealed a red-cell count of 3,950,000, with a hemoglobin of 11.5 gm. per 100 ml. and a hematocrit of 45 mm., and a white-cell count of 18,500, with 80 per cent neutrophils. The corrected sedimentation rate was 10 mm. per hour. Electrocardiographic findings were consistent with an extensive infarction of the anteroseptal wall. There were some premature ventricular contractions, which were absent on subsequent tracings.

During the 1st hours in the hospital, the patient complained of chest pain and nausea, but she appeared quite comfortable. Ten hours after admission, she suddenly went into shock, with typical ashen-gray color, profuse, clammy perspiration and cold extremities. The pulse and blood pressure were unobtainable. Treatment was begun with mephentermine sulfate,§ a pressor amine, given intravenously for the 1st 2½ hours, and subsequently intramuscularly in 15-mg. doses every ½ hour. The blood pressure and pulse were checked every ½ hour.

For more than 30 hours, the blood pressure was unobtainable. The pulse was impalpable for the 1st 10 hours, and then it was found to be weak, with a rate of 100. The 1st blood-pressure reading to be obtained was 82/?. Two hours later the pressure was again unobtainable, and remained so for a further 12 hours. During this time the patient either rambled incoherently and complained of chest pain, or dozed quietly. Respirations were labored. The temperature ranged around 102°F. Sixty milliliters (2 ounces) of urine was obtained by catheter in the 1st 36 hours after the onset of shock.

Thus, except for a short interval of 2 hours, the blood pressure was unobtainable for a total of over 40 hours. The 1st reading recorded was 120/60, and the pressure remained at about this level for the next 24 hours. It then rose to 140/115. Mephentermine was then discontinued, and the pressure stabilized at about 120/80. With the rise in pressure there was a return of urinary output, 210 ml. being passed in 24 hours. Roughly the same amount was passed the next day, when the blood creatinine was found to be 12 mg. per 100 ml. Thereafter, the urinary output increased progressively, reaching 1320, 1350 and 1500 ml. during the last 3 days before death. Electrocardiograms showed serial changes of an acute infarction, with no apparent extension of the process. The rhythm remained regular. Despite improvement in several respects, the patient's condition continued to be precarious. The extremities remained cold despite a flushed face and a temperature of 102°F. by rectum. On the morning of the 4th hospital day, some 80 hours after the onset of shock, it was first noted that the tip of the nose, fingers and toes were very cyanotic. The cyanotic areas slowly spread, and by the 7th day had progressed to superficial gangrene symmetrically involving the toes, soles and heels, fingers, and end of the nose. The pulses were not palpable in the feet, but the femoral and radial pulses were present.

With the onset of gangrene, the general condition remained essentially the same. At times the patient responded to questions, and on 1 occasion, she was described as being alert and conscious. For the most part, her mental state was one of delirium. The blood pressure, surprisingly

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§Available as Wyamine from Wyeth Laboratories, Philadelphia.

enough, remained usually at about 128/76, so that few injections of mephentermine were necessary. Respirations, generally, were labored. On the 10th hospital day, her color suddenly became poor, and her pulse unobtainable. The usual therapeutic measures were of no avail, and she died within 2 hours. Apart from the mephentermine, the therapy included oxygen, morphine sulfate, barbiturates, papaverine, 2 small blood transfusions, anticoagulants and infusions.

At autopsy the heart weighed 380 gm. There was a thrombotic occlusion of the left anterior descending coronary artery. Changes of infarction affected the anterior and anterolateral wall of the left ventricle and the anterior half of the interventricular septum. There was a small, irregular, linear perforation near the apex of the left ventricle, and the pericardial sac was filled with blood. The lungs were

FIGURE 1. *Post-Mortem Appearance, Showing Gangrene of the Tip of the Nose.*

markedly hyperemic, but no significant edema of the parenchyma was apparent. The liver weighed 1020 gm. On section, the cut surfaces showed prominent lobular markings due to distinctly reddened central lobular zones. The adrenal glands were normal in size, shape and appearance. Each kidney weighed about 160 gm.; on section, the cut surfaces were moderately hyperemic. The cortex and medulla were of average width and showed regular markings. Both hands and feet and the tip of the nose demonstrated the changes already described (Fig. 1 and 2).

DISCUSSION

This type of peripheral gangrene, as would be expected from its characteristic strikingly symmetrical distribution, has been shown not to be due to embolization. The exact hemodynamics remain obscure, but it is known that shock after myocardial infarction is associated with marked diminution of cardiac output.

Blalock and his associates[8] demonstrated that the reduction in flow from the various areas of the body is not the same in shock. The degree of vasoconstriction present is not uniform. Hence, the venous pressure in the external jugular vein may not be equal to the reading obtained in the antecubital vein. Fishberg[9] interpreted this discrepancy as evidence of preferential vasoconstriction on the part of the body in its attempt to divert blood to the brain and other vital organs. There appears to be preferential vasoconstriction in the skin, spleen, liver and kidney.

In the case described above, the peripheral vasoconstriction persisted in the skin, but apparently not in the kidneys. The initial anuria and then marked oliguria might be construed as indicating a sharp decrease in renal blood flow from diminished cardiac output and vasoconstriction. The ensuing events are interesting, in that the urinary output, in the last three days before death, returned practically to normal despite the onset and progression of gangrene peripherally. The inference might be drawn that in shock after myocardial infarction, the body may preferentially relax as well as constrict the peripheral vascular system.

The degree of shock in this case was most pronounced. One wonders why the mechanisms resulting in "irreversible" shock[10] did not ensue. Apparently, there is no definite time limit beyond which shock becomes irreversible. Possibly, the occurrence of symmetrical peripheral gangrene indicates that the protective mechanism of peripheral vasoconstriction is acting maximally. This might explain the surprising temporary recovery, with return of the blood

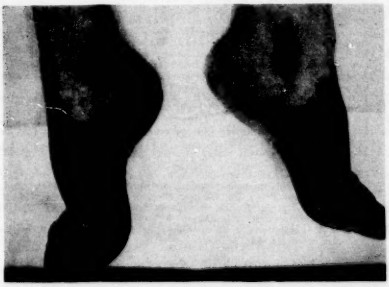

FIGURE 2. *Post-Mortem Appearance of the Feet, Showing the Changes Described.*

pressure to normotensive levels, after an excessively long period of profound hypotension. The fact that the vasopressor drugs may act in a way similar to that of a natural "protective" mechanism might explain their general enthusiastic acceptance. If this is so, it might seem reasonable to potentiate their action in selected cases with the use of drugs such as ACTH and cortisone.[11]

The part that mephentermine played in precipitating the peripheral gangrene is questionable. In previous similar cases reported in the literature vasopressor drugs were not given. The action of mephentermine is transient and tachyphylactic. Intense cyanosis of the peripheral parts of the body did not begin until the day after the drug had been discontinued. Nor-epinephrine, another vasopressor drug,

has been given as a continuous intravenous drip for twenty days in myocardial infarction with shock, without unfavorable peripheral effects.[12]

Although few cases of symmetrical peripheral gangrene complicating myocardial infarction have been presented, the condition may be more frequent than the reports indicate. Indeed, in a recent article on shock in myocardial infarction, Selzer[13] records in passing the appearance of peripheral gangrene in a "typical" illustrative case. We believe that these cases may throw some light on the subject of shock in myocardial infarction by exhibiting in extreme degree changes that usually take place to a lesser extent.

Summary

A case of symmetrical peripheral gangrene occurring in myocardial infarction with extreme shock is presented. Some features of the mechanism are discussed.

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SIGNIFICANCE OF AN OPAQUE, GREEN BENEDICT REACTION

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BOSTON

DOES an opaque, green Benedict reaction "mean anything"? This question persists. A series of 1000 such reactions correlated with the fermentable sugar in each case now sheds some light on the question without, unfortunately, wholly answering it.

The fermentable sugar ranged from none to 0.72 per cent (Fig. 1). The figures are condensed into a much simpler form in Table 1.

Since as much as 0.05 per cent of fermentable sugar may be present in a urine that gives a completely negative Benedict reaction, it thus appears, as commonly supposed, that the majority of opaque, green Benedict reactions mean nothing. Interesting as this disclosure may be, unhappily it is of no help when one is suddenly confronted with such a reaction. And, except by fermenting the urine and repeating the test, I know of no way of determining if the reaction was caused by glucose.

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Appearance of Reaction

The appearance is not reliable. It is true that Peters and Van Slyke[1] have stated that positive copper reduction tests due to substances in normal urine besides glucose are not rare, adding, "The experienced analyst may detect them at times by noting that the precipitate formed during the qualitative test with Fehling's or Benedict's solution is unusual in its appearance or manner of development." However, with every sympathy with that statement, I must say that after thirty-five years I still cannot always be sure even when consciously trying to guess correctly.

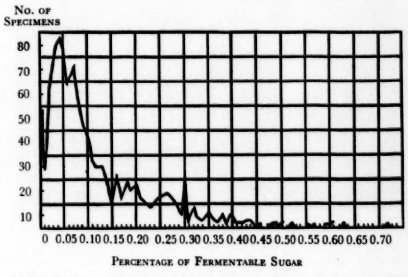

FIGURE 1. *Fermentable Sugar in 1000 Opaque, Green Benedict Reactions.*

Nonglucose Sugars

Undoubtedly, in specimens from female subjects, some of the reactions indicated lactose, although never identified. There is no simple, specific test for lactose. On the other hand, such specimens often contained fermentable sugar. It is not safe to assume that a green reaction on a specimen from a female patient indicates lactose.

Also, it should be noted, green reactions caused by the rare pentose sugar in several cases were indistinguishable except, perhaps, that pentose reactions begin to appear surprisingly quickly.

Nonsugar Reducing Substances

Their nature was not determined. Various possibilities may be ascertained from textbooks. After examining several I believe that they often merely repeat each other and have little corroborative value.

Phenylhydrazine Test

This test, once highly regarded, was done on all specimens. It gave many atypical, apparently false-positive reactions. It should be noted that Everett and Sheppard[2] have explained its fallacies, particularly its tendency to react with urea as well as with sugars. It is valueless routinely at the concentration of reducing substances under discussion. Nor is it a convenient test to do. And, incidentally, 2 of the technicians in this laboratory seem to have been sensitive to phenylhydrazine, troublesome skin eruptions developing on the hands and suggesting athlete's foot.

Time in Boiling-Water Bath

Benedict[3] never specified a boiling-water bath. His directions were to boil over the naked flame for three minutes.[3] How five minutes in a boiling-water bath got into the literature is a mystery. Dr. Albert A. Hornor, of Boston, recalls that many years ago, in Dr. Joslin's laboratory at the New England Deaconess Hospital when it was decided to do Benedict's test en masse, the question arose how long in boiling water would be equivalent to three minutes over the flame; Dr. Hornor "guessed perhaps five minutes." And five minutes was adopted. That may be the origin. At any rate, boiling for much longer than five minutes develops many false-positive green reactions. With Exton's[4] evidence that nonsugar reducing substances are slower in showing reactions than the sugars, four-minute and even three-and-a-half-minute intervals have been experimented with in the hope of eliminating the nonsugar reactions, but without success. Evidently five minutes is the optimum boiling time.

Fermentation

All specimens were fermented in an open test tube in a water bath at approximately 96°F., about equal parts of urine and baker's yeast being taken; 4 or 5 ml. of urine is sufficient. At this concentration all the glucose that gives a green Benedict reaction is destroyed in ten or fifteen minutes, when the emulsion may be cleared by centrifuging and the Benedict test repeated. Thus, even in a doctor's office, a questionable reaction may be checked quickly and possibly save a patient the bother — indeed, even the worry — of submitting a second specimen. In life-insurance work, where specimens come to the home office from quite distant cities, even from the Hawaiian Islands, it is important to avoid requesting a second specimen if possible, and all doubtful reactions are checked. Over the past dozen years it appears from the records of this laboratory that 7396 persons with questionable reactions have been saved from a suspicion of sugar, as well as from much unnecessary expense, bother and worry.

It should be noted, in passing, that baker's yeast in 1-pound and ½-pound packages is pure and remains potent for weeks in the refrigerator. The small 4-cent or 5-cent cakes in the past contained added substances that reacted with sugar tests. A dry yeast on sale at grocery stores is less potent, but effective if fresh. However, in the presence of formaldehyde its fermenting power is slowed down considerably, and when it is very old, considerable reducing substances develop.

The quantitative sugar procedure has been the Benedict picrate method[5] before and after fermentation. By this method readings may be made virtually to a hundredth of a per cent even without a colorimeter, merely by side-by-side comparison of the unknown with a set of color standards.

Table 1. *Condensed Figures for 1000 Opaque, Green Benedict Reactions.*

Percentage of Fermentable Sugar	No. of Specimens	Percentage of Specimens
0 - 0.09	573	57
0.10 - 0.19	220	22
0.20 & over	207	21

Clinitest and Galatest

These ingenious tests are excellent within the limits of their instructions. In the presence of traces of reducing substances their reactions correspond pretty closely to the Benedict opaque, green reaction. The Clinitest gives fewer false-positive reactions but compensates by occasionally missing a trace of true sugar. The Galatest is particularly sensitive to traces of formaldehyde, as, indeed, the instructions warn. Although not quite as easy to read as Benedict's reactions, both may be used before and after fermentation, with quite good results.

Conclusions

An opaque, green Benedict reaction means nothing in the majority of cases. However, whenever it is significant, as when it indicates upward of 0.6 or 0.7 per cent glucose, mere inspection of the reaction will not differentiate. The only expedient is rapid fermentation, and a repeat test.

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CASE RECORDS
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CASE 42121

PRESENTATION OF CASE

A twenty-one-month-old girl was admitted to the Memorial Hospital, Worcester, because of hematuria.

Since birth the child had not gained weight normally, but her appetite had been good, and the stools had been normal. She had been troubled with eczema and had been on a fat-free diet. When she was seven months old roseola developed. At the termination of this illness, she had convulsions that lasted six hours; subsequently, the left side was paralyzed for two months. However, she regained full motion and power and seemed well afterward. Two weeks before admission she had a cold, with cough, nasal discharge and intermittent fever that usually increased at night. A cough medicine and aspirin were prescribed. Two days before admission the mother noticed that the child began to pass "more or less pure-red blood" in the urine and had pain on micturition.

Physical examination showed a well developed, fretful, pale infant with a "puffy" face and without signs of dehydration. The weight was 18 pounds, 8 ounces. Examination of the head, neck, heart and lungs was negative. In the right flank, an orange-sized, firm, tender, slightly movable mass was palpable. The left kidney was enlarged and tender and extended well into the abdomen. The liver and spleen were not felt. The examination of the extremities and the nervous system was negative.

The temperature was 99°F., the pulse 140, and the respirations 20. The blood pressure was 98 systolic, 72 diastolic.

The urine was alkaline and gave a +++ test for albumin and a ++ test for acetone; the sediment contained 4 to 6 white cells, a great many red cells and a few faintly granular casts per high-power field; culture grew alpha *Streptococcus faecalis*. Examination of the blood showed a hemoglobin of 9.4 gm. per 100 ml., a hematocrit of 32 per cent, a red-cell count of 3,400,000 and a white-cell count of 17,950, with 74 per cent neutrophils, 22 per cent lymphocytes and 4 per cent monocytes. The red cells varied slightly in size, with a tendency to microcytosis. The nonprotein nitrogen was 122 mg., the phosphorus 12.4 mg., and the calcium 8.7 mg. per 100 ml., and the carbon dioxide 18.4 milliequiv. per liter.

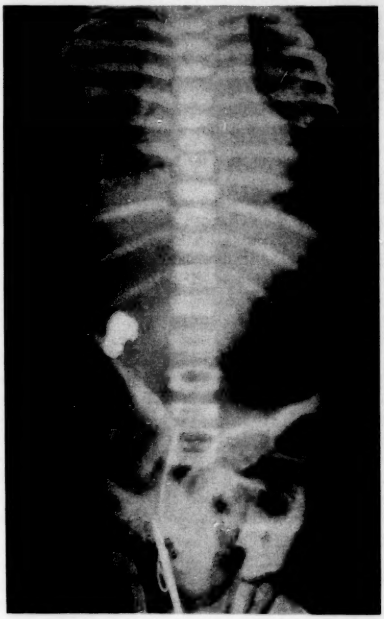

FIGURE 1.

Roentgenograms of the abdomen demonstrated a large soft-tissue mass having the shape and position of the kidney in the right flank (Fig. 1). No calcification was seen within it. The region of the left kidney was obscured by gas-containing loops of small intestine. The left kidney was thought to be slightly enlarged, but its outlines were too indistinct for evaluation. X-ray films of the chest were normal. The bones were decalcified, without cystic change or abnormalities in the epiphyses or epiphyseal lines. Shortly after admission, an intravenous pyelogram after administration of 2 ml. of Hypaque showed no excretion of the dye on either side during a period of two hours. On some of the films the left kidney was faintly visualized and again appeared to be slightly enlarged.

On the day after admission a cystoscopic examination was performed. The urine in the bladder was bloody, but the mucosa of the bladder was normal. Blood exuded from the orifice of the right ureter; that of the left appeared normal. A No. 4 catheter passed up to the right kidney, but a catheter would not pass the orifice of the left ureter. At this point, acute pulmonary edema developed, and the procedure was terminated. The pyelogram on the right side demonstrated filling of a dilated superior calyceal group with a faintly opacified linear collection of dye extending downward from it that possibly represented an elongated infundibulum or a narrowed superior pelvis of a double kidney. The upper end of the right ureter had an elongated filling defect at its communication with the questionable superior infundibulum. A few fine streaks of dye were seen to extend from the superior ureter laterally toward the main renal mass, but there was no filling of a normal-appearing renal pelvis or of any other calyxes. The margins of the mass in the right flank were not defined and were not separable from the liver shadow. Neither psoas shadow was well visualized. On return from the operating room, the child was pale, and the respirations 60. She was placed in an oxylator at 6 liters. Subsequently, she passed a tarry stool, the respirations became labored at a rate of 72, with retraction of the interspaces and frothing at the mouth. Death occurred eighteen hours after the cystoscopic examination.

Differential Diagnosis

Dr. Frederic M. Blodgett*: The pediatrician following children and their illnesses has one advantage in appraising the nature and the chronicity of the disease — namely, the ability to observe the effect of the illness on the growth of the child. This patient was described as well developed; yet her weight was only 18½ pounds. This would be a normal weight for a well developed child of ten months, but for a twenty-one-month-old child it certainly was grossly underweight. I wonder, therefore, if there are any measurements that would indicate the rate of linear growth in this child?

Dr. Ronald C. Sniffen: No.

Dr. Blodgett: I assume, then, that if to the examiner she appeared well developed at this weight she had not undergone a normal rate of linear growth, because at a normal length she would have appeared emaciated.

The positive findings were a firm, orange-sized, slightly tender, movable lesion in the abdomen and a left kidney that was directly described as palpable. It is unusual for a kidney to be palpated so easily. One wonders indeed whether the kidney was enlarged, or whether the abdominal wall was so depleted in fat and muscle that the kidney was easier to palpate; therefore, the examiner interpreted it to be enlarged.

The face was puffy, but no edema of extremities was noted and there was no hypertension. Consequently, I am somewhat at a loss to determine whether the puffiness indicated edema or not. The laboratory data certainly gave direct evidence of renal disease, with hematuria, albuminuria, acetonuria, nitrogen retention and hyperphosphatemia in the presence of acidosis suggested by the depressed carbon dioxide. Furthermore, the x-ray films revealed that the mass on the right side of the abdomen and the right kidney might be the same structure. In addition, there was distortion and a filling defect of the calyceal system on the right. May we look at the x-ray films?

Dr. Paul M. G. St. Aubin: The x-ray films of the chest appear normal. In answer to the questions about tissue edema, the x-ray film does show definite swelling throughout the subcutaneous soft tissue. The bones appear generally demineralized but not markedly so; there is no evidence of any other bony abnormality. The film of the abdomen taken on admission shows a mass in the right flank that has a well defined, rounded lower margin; the mass certainly has the appearance of an enlarged lower pole of the kidney. In the lateral projection there appears to be a large mass in the position of the kidney, presumably on the right side. There are two films from the intravenous pyelogram for which 2 ml. of contrast substance was given.

Dr. Blodgett: Is that an adequate amount of this particular medium?

Dr. St. Aubin: Under ideal conditions of dehydration the renal excretory system can be outlined satisfactorily with this amount. It certainly was not ideal in the present study. No contrast substance is seen in the renal collecting system. The left kidney certainly appears enlarged. The retrograde pyelogram of the right side demonstrates dilatation of what appears to be the superior-pole calyceal system. The long, narrow column of contrast substance seen below this system probably represents the infundibulum of the superior pole, and a portion of the right ureter is seen above the tip of the catheter. Within the pelvis is a wormlike filling defect, which is not the catheter. There is probably some contrast substance in the lower-pole calyceal system, but this opinion is not absolutely certain since there are equally dense areas between gas-filled loops of bowel on the left side.

Dr. Blodgett: There is some distortion of the kidney pelvis on the right side at least. Does this thin streak suggest the so-called spider sign that is thought to be typical of a tumor of the Wilms type in a distorted pelvis?

Dr. St. Aubin: I do not believe that it does. This appearance can result from the passing of contrast substance up through a narrowed infundibulum in a state of spasm.

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DR. BLODGETT: There is decalcification of the bones without changes of the epiphyses.

DR. ST. AUBIN: That is correct. The decalcification is not striking. These final films show marked pulmonary edema in both lung fields.

DR. BLODGETT: In a child of this age group, with a mass in the abdomen, it is a safe clinical rule to consider such masses malignant tumors until the possibility can be completely dismissed, for those conditions demand careful handling and immediate specific therapy. Therefore, I must ask myself if this was a malignant tumor, such as a Wilms tumor, or invasion of the kidney from an adrenal tumor. Several features suggest that a malignant tumor of the kidney is not completely compatible with the progress of the illness. The first rests on the assumption that the child may have been retarded in her growth — indeed, she certainly seems to have progressed poorly since the time of her birth. Generally, the child in whom a malignant tumor develops at this age is in a reasonably good stage of nutrition until a short time before the tumor makes itself known. In addition this child did not have hypertension. Of course, not all malignant tumors involving the kidneys produce hypertension, but in many series 75 to 95 per cent of the children with Wilms's tumors have had hypertension. The hematuria is often found with malignant tumors of the kidneys but is generally not of the degree that would be described as the passage of almost pure-red blood. One would then be somewhat less anxious to make a diagnosis of malignant tumor.

In thinking of the nature of the renal disease, one is impressed by the evidence of acidosis as determined by the carbon dioxide; yet the urine was alkaline. This seems to be an inappropriate way for the kidneys forming the urine to respond; one would think that the kidneys would serve the body better if they produced an acid urine. I assume, therefore, that there was a defect of the kidneys that kept them from responding more appropriately. In addition there was evidence of renal disease in the retention of the phosphorus and perhaps the mild depression of the calcium. The elevation of the nonprotein nitrogen was confirmatory evidence of a severe degree of tubular and probably glomerular damage. Consequently, one gives attention to the types of renal disease that might be present for some time and show these features. Among them infection of the urinary tract takes high precedence. In the presence of cultures on this child's urine, which grew out alpha *Str. faecalis,* the suspicion of infection would be high. Furthermore, roseola, as the pediatrician usually sees it, is perhaps a four-day illness of high fever. Usually, if there is central-nervous-system involvement and a febrile or other type of convulsion, the convulsion occurs at the onset of the disease, not at the end of it. Consequently, one is hesitant to say that roseola explained the convulsions. One would wonder if renal involvement, along with the consequence of the illness, upset her ability to defend herself from hypocalcemia and if, therefore, after a period of alkalosis, she had a convulsion secondary to hypocalcemia.

Finally, the bones showed some demineralization. Is this compatible with the renal disease? If she had acidosis for some time and if there was elevation of the phosphorus and other signs of kidney disease, this may have been one of the early phases of osteitis fibrosa (the older term is renal rickets), of a mild nature, perhaps. Why did she not show the changes of rickets? It is possible that the child's growth had been impaired for some time; indeed, the changes of rickets are dependent on growth at the epiphyses. The absence of rickets does not mean the absence of the potential for it; the evidence of it might have shown up if there had been more linear growth of the bones. I should choose a congenital defect of the kidneys in which infection had taken place to explain the renal picture. It would be possible for one of the metabolic diseases involving the kidney, such as cystinosis, to have accounted for many of the renal findings, the stunting and the changes in the bones. Cystinosis, which is closely related to and at times hard to differentiate from the de Toni–Fanconi syndrome, in which there is hypophosphatemia, must remain a consideration.

The mass was one of the principal findings. The possibility that I am not entirely able to dismiss is tumor. There remains the other possibility that this was a congenital type of renal abnormality — polycystic kidney disease or a single cystic disorder. There was evidence from the x-ray films, although not great, that there was bilateral renal enlargement. There was not, however, in the x-ray films, the renal distortion of pelves to the extent that one would expect.

The child died, quite unexpectedly I take it, having had an episode of pulmonary edema. What could have led to the pulmonary edema? Certainly, during the process of cystoscopic examination, the physician tries to ensure an adequate output of urine. This means the infusion of fluid intravenously that at times gets out of control. I wonder if this patient was receiving fluids intravenously during the cystoscopic examination?

DR. SNIFFEN: I do not know.

DR. BLODGETT: Certainly, the renal disease she presented did not suggest that death was imminent at the time of cystoscopy; its occurrence during the procedure strongly suggests that infusion of fluid was directly related to the precipitation of pulmonary edema. In the type of renal diseases that we have talked about there is always the possibility of excessive loss of potassium. During hypopotassemia it might be easier to produce cardiac embarrassment, pulmonary edema and circulatory failure by the infusion of fluid. The death seems directly related to

the episodes of pulmonary edema. I believe that she may not have recovered from the episode of pulmonary edema as suggested by the findings and that the death was attributable to that.

The hematuria still bothers me. We do occasionally see hematuria in children in the absence of tumors and in the absence of severe dysuria. Under these circumstances hematuria in our patients has usually been related to infection. I think, therefore, that the mass in the kidney represented a congenital abnormality that had been present since early infancy and had become infected during its course, rather than a malignant tumor. The renal changes were those secondary to infection and the basic abnormality.

DR. BENJAMIN CASTLEMAN: What kind of abnormality do you mean—polycystic disease of the kidneys?

DR. BLODGETT: Either polycystic disease or one of its variants.

DR. LEWIS KANE: Is the heart enlarged or of normal size in the x-ray film?

DR. ST. AUBIN: It is normal.

DR. KANE: Is the normal size of the heart consistent with edema due to overhydration?

DR. BLODGETT: We see that phenomenon during the course of cystoscopic examination with the infusion of fluid; I think that that was the most likely possibility. There was no previous evidence of cardiac disease in this child, to be sure, but it is possible that in some metabolic diseases the heart is susceptible to difficulty.

DR. SNIFFEN: Can you explain the paralysis after roseola?

DR. BLODGETT: I cannot say with certainty the cause of the convulsions. I shall have to say that, with a febrile seizure of long duration, a transient hemiparesis or some other neurologic sequela may occur.

DR. SNIFFEN: I have no answer for it either.

CLINICAL DIAGNOSIS

?Polycystic disease of kidneys.
?Wilms's tumor, bilateral.

DR. FREDERIC M. BLODGETT'S DIAGNOSIS

Congenital abnormality, ?polycystic disease of kidneys, with infection.

ANATOMICAL DIAGNOSES

Wilms's tumor of kidney, bilateral.
Subacute glomerulonephritis.
Bronchopneumonia.

PATHOLOGICAL DISCUSSION

DR. SNIFFEN: At autopsy a distinctly unusual state of affairs was encountered. The immediate cause of death was extensive acute hemorrhagic pneumonitis that must have developed after the chest film was taken less than two days before death; presumably, it was present during the time of cystoscopy.

The lower pole of each kidney was destroyed by a sharply circumscribed, somewhat lobulated tumor with a pale, glistening, homogeneous cut surface. The tumor on the right measured 10 cm. in diameter and that on the left 5 cm. in diameter. Both were in intimate contact with the calyxes and pelves. The renal vessels were not invaded by the neoplasm. About half the renal parenchyma was destroyed on each side. Microscopically, these masses were classic Wilms tumors composed of small, deeply chromatic, spindle cells with the formation of glomerulotubular structures resembling the primitive renal blastoma. No other elements, such as smooth muscle and striated muscle, were identified in the tumors. Metastatic deposits were not found. Bilateral Wilms tumors are distinctly uncommon, although the unilateral variety accounts for about 25 per cent of all neoplasms in childhood and is practically the only malignant tumor of the kidney in children.

Equally intriguing and undoubtedly the reason for the high nonprotein nitrogen, apart from obvious signs of focal pyelonephritis, was a diffuse proliferative glomerulitis involving the remaining parenchyma. Each glomerulus was ischemic and showed swelling and hyperplasia of the endothelial and epithelial cells. These changes were associated with epithelial crescent formation, occasional necrosis of a capillary loop and thickening of the basement membrane of the glomerular capillaries. The convoluted tubules were usually dilated, and some of them showed papillary infolding. Many granular eosinophilic casts were present, and the cells of some of the proximal convoluted segments contained large hyaline droplets. There were no visible abnormalities in the extraglomerular vessels. In brief, these were the changes of subacute diffuse glomerulonephritis.

CASE 42122

PRESENTATION OF CASE

A sixty-four-year-old Negro, who worked in a scrap-iron yard, entered the hospital because of weakness.

Three and a half months previously there was an episode of syncope associated with a smothering sensation in the right side of the chest. Several days later the patient noted postprandial right-sided epigastric distress that lasted for two weeks. Two and a half months before entry the temperature was noted to range between 99.4 and 101.2°F. Examination of the blood revealed a hemoglobin of 9.2 gm. per 100 ml. and a white-cell count of 11,300. The serum iron was 105 microgm., the nonprotein nitrogen 37 mg., and the fasting blood sugar 104 mg. per 100 ml. The blood Hinton test was negative. The urine gave a +

test for albumin. An upper gastrointestinal series demonstrated thickened gastric mucosal folds with several minute ulcerations along the lesser curvature and a probable deformity of the duodenal bulb. A film of the chest showed an enlarged heart and elongation of the aorta. Barium-enema and sigmoidoscopic examinations were negative. Two stools gave negative guaiac tests. During the two months before admission there was a dull, aching, postprandial paraumbilical pain occurring every two or three days associated with flatulence and constipation and relieved by milk of magnesia or mineral oil. In spite of iron therapy and an ulcer regimen, there was progressive weakness, anorexia and a 20-pound weight loss. There was no melena, jaundice or change in the caliber of the stools.

FIGURE 1.

Physical examination revealed an asthenic man with evidence of recent weight loss. The left border of cardiac dullness extended 2 cm. beyond the midclavicular line in the sixth intercostal space. Abdominal and rectal examinations were negative.

The temperature was 100.8°F., the pulse 80, and the respirations 16. The blood pressure was 125 systolic, 85 diastolic.

Examination of the blood showed a hemoglobin of 8.5 gm. per 100 ml. and a white-cell count of 19,400, with 80 per cent neutrophils. The erythrocytes were hypochromic, and there was marked thrombocytosis. The bone marrow revealed an increased number of megakaryocytes and 20 per cent mature plasma cells. The serum nonprotein nitrogen was 34 mg., the total protein 8.3 gm., the albumin 4.4 gm., the globulin 3.9 gm., the iron 70 microgm., the calcium 9.2 mg., the phosphorus 4.7 mg., and the bilirubin 0.3 mg. per 100 ml. The alkaline phosphatase was 12.2 units, and the acid phosphatase 1.3 units total and 0.2 units prostatic. Cephalin flocculation was negative in forty-eight hours. Thymol turbidity was 1 unit, and flocculation was negative. The serum electrophoretic pattern was normal except for a slight increase in gamma globulin. The Coombs test was negative, as were heterophil-antibody, typhoid, paratyphoid and brucella agglutination tests. Second-strength PPD skin test for tuberculosis was positive in forty-eight hours. Blood cultures showed no growth. The urinary sediment contained 3 or 4 white cells per high-power field. Urine cultures grew out rare coliform bacilli and a few nonhemolytic streptococci. Numerous stool specimens gave a negative guaiac test. An upper gastrointestinal series showed enlarged gastric mucosal folds and a somewhat deformed duodenal bulb. Intravenous pyelograms were unsatisfactory. Retrograde pyelograms showed some distortion of the calyceal system of the lower pole of the right kidney, and there appeared to be a pressure defect in the inferior portion of the pelvis (Fig. 1); examination of the left kidney was negative. Films of the chest, pelvis, skull and spine were normal except for degenerative changes in the lumbar spine. An electrocardiogram was suggestive of left ventricular hypertrophy. Cytologic examination of the gastric juice was unsatisfactory. Gastroscopic and sigmoidoscopic examinations were negative.

A biopsy of the liver showed no abnormalities. Bone-marrow biopsy showed no granulomas or tumor cells. In spite of antibiotic therapy the temperature remained elevated, ranging between 99 and 102.4°F. On the fifty-sixth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. VICTOR G. BALBONI*: Progressive weakness, weight loss, anemia and fever in a sixty-four-year-old man suggest either malignant neoplasm or chronic infection.

This patient had experienced epigastric distress after meals, and the x-ray studies gave evidence of gastritis and small ulcers on the lesser curvature of the stomach. He was put on an ulcer regimen, but the course was steadily downhill. Three and a half months after the onset of the illness, when he was admitted to the hospital, the physical examination confirmed the weight loss and the presence of fever and added the finding of an enlarged heart. He had anemia so that in the absence of other evidence of heart disease, it seems reasonable to assume that the enlarged heart was secondary to the anemia. Among the malignant processes that could produce this picture are carcinoma (either in the stomach or possibly in the pancreas), myeloma and lymphoma.

*Assistant physician, Massachusetts General Hospital.

Among the chronic infections that this patient may have had are tuberculosis, brucellosis and the enteric infections. He may have had a subacute bacterial endocarditis or endarteritis. In patients in this age group an infection occasionally arises on an arteriosclerotic plaque in the aorta. I assume that he did not have a valvular lesion — at least none was described in the protocol; therefore, one might consider the rare possibility of a bacterial aortitis.

With these diagnostic possibilities in mind I shall turn to the laboratory data for help. There was a hypochromic anemia and a moderate leukocytosis. Ordinarily, we think of hypochromic anemia with low serum iron as occurring in a man only in the presence of blood loss, but there was no evidence that this man had lost any blood — at least the stools were normal. However, in patients with chronic infection, as well as in those with a widespread neoplastic process, a hypochromic anemia with low serum iron can develop, so this finding gives me little help. A + test for albumin in the presence of a temperature up to 102°F. is not very helpful, for it could occur without any kidney lesion. The few organisms grown out on the urine culture I consider insignificant, and I interpret this culture as ruling out the kidneys as a source of infection. Blood cultures were also negative so that I think it is fair to say that the patient did not have a bacterial infection of the blood stream. The agglutinations for typhoid, paratyphoid and brucella, and the heterophil-antibody agglutinations, although not always 100 per cent accurate, fairly well rule out the infections for which they were performed. An x-ray film of the chest gave no evidence of tuberculosis. There is very little in the laboratory data to suggest infection; in fact most of the data other than the leukocytosis are against infection so I think that I can rule it out as the cause of this man's illness.

A third possibility is one of the "group diseases," which we always have to consider in patients who have fever of unknown cause. By "group diseases" I mean disseminated lupus erythematosus, polyarteritis nodosa, dermatomyositis, scleroderma and rheumatoid arthritis. These diseases almost invariably have some musculoskeletal symptoms, and this man had none. In the total course there was very little other than fever and anemia to suggest any of the "group diseases."

I am now left with a diagnosis of malignant neoplasm. I imagine that the Service thought he had a neoplasm and probably performed certain x-ray studies to locate its source. I should like to ask Dr. Wyman to show the x-ray films.

DR. STANLEY M. WYMAN: From a number of examinations done during the fifty-six days this patient was in the hospital, I have tried to select representative examples. The lungs are clear. The heart is enlarged; this may be in part produced by the anemia. There is nothing to suggest a tumor in the lungs, and there is no evidence of tuberculosis. The bones of the thoracic cage are rather dense; they are homogeneous, but more dense than one would expect in a man of sixty-four, particularly one who had been sick for this length of time. I do not see any localized destruction. The gastrointestinal examination demonstrates diffuse prominence of the gastric rugae and fine serration along the lesser curvature. I do not think this serration is a finding to which one can attach much significance. It is seen with gastritis and with other conditions, but it is nonspecific and not impressive in this particular case. The deformity of the duodenal cap is not classic, but I think it is consistent with an old ulcer. Something pushing the cap from outside, however, would produce the same appearance. The degenerative changes in the spine are well seen, and here again the bones are unusually dense. In the one film from the barium-enema examination, the colon shows no intrinsic abnormality. The hepatic flexure is lower than one expects, so one might wonder if something was pushing it down, but I see no evidence of invasion of the colon. In the last films from the retrograde examination of the kidneys, the left kidney seems to be normal; on the right the lower pole of the kidney is displaced laterally, and there is a definite suggestion of indentation and pressure on the undersurface of the pelvis so that one certainly wonders about a mass in or adjacent to the lower pole of the kidney (Fig. 1). I can go no farther than that. There is no invasion of the calyceal system.

DR. BALBONI: Could that be a retroperitoneal mass pressing on the kidney?

DR. WYMAN: Yes; it perfectly well could be. Any retroperitoneal mass could rotate the kidney in this fashion. I cannot outline the kidney well enough to say whether this mass arose in the kidney or adjacent to it.

DR. BALBONI: Are Negroes more prone to have dense bones than white men?

DR. WYMAN: I do not believe so. This man was a worker in a scrap-iron yard; I assume he did heavy manual work, which may account for the fact that his bones were well mineralized. In those who use their bones actively there is a high degree of mineral content. Of course, in Negroes one always considers sickle-cell anemia, which produces a diffuse density of bone, but that is a very tenuous suggestion.

DR. BALBONI: The x-ray studies, although they do not make a definitive localization of the patient's disease, suggest either that there was involvement of the kidney by some intrinsic malignant lesion or that enlarged lymph nodes pressed upon and distorted the kidney. There was also a suggestion of an enlarged lymph node in the area of the duodenum. This man had no symptoms to suggest a duodenal ulcer, so that I prefer to interpret the deformity of the duodenal bulb as being the result of an enlarged lymph node. It fits my diagnosis better.

A review of the special studies undertaken to try

to clarify the diagnosis may be helpful. Smears of gastric washings were examined for tumor cells; unfortunately these studies were unsatisfactory. Gastroscopy was then performed, and the stomach looked normal to the gastroscopist. A bone-marrow biopsy showed 20 per cent plasma cells; this is a most unusual finding. Plasma cells ordinarily do not make up more than 1 or 2 per cent of the cells in a bone marrow. Almost any condition that causes an increased globulin in the blood may be accompanied by an increased number of plasma cells. I have heard of a case of rheumatoid arthritis with hyperglobulinemia in which the number of plasma cells in the marrow was increased. However, the increase in plasma cells in the patient under discussion is striking and much higher than is usual in patients with infection or with arthritis; it certainly suggests the possibility of plasma-cell myeloma. The megakaryocytes in the bone marrow were also increased. At this point I should like to ask if the bone-marrow biopsy confirmed the presence of an increased number of plasma cells and of megakaryocytes.

Dr. Robert E. Scully: The megakaryocytes and plasma cells were both somewhat increased in number in the biopsy specimen.

Dr. Balboni: I still do not have much help from the laboratory studies although the increased number of plasma cells suggests myeloma. It is also well to bear in mind that in bone-marrow studies it is very difficult to distinguish a megakaryocyte from the Reed–Sternberg cell of Hodgkin's disease, unless special stains are done. The high total protein and the high-normal albumin are against infection, for in chronic infection the albumin usually decreases. This is also against liver disease. The globulin was definitely elevated and would go with multiple myeloma or lymphoma. The proteins were studied by electrophoresis and were reported as showing a normal pattern with increase in the gamma globulin. I hope that Dr. DuToit will tell us later what he thinks of the usefulness of paper electrophoresis in differential diagnosis. The alkaline phosphatase was definitely elevated. In the presence of bone disease, particularly metastatic neoplasm in the bones, it would be elevated, but the skull films were normal and there was nothing in the other x-ray films to suggest a metastatic neoplasm. The alkaline phosphatase could also have been elevated if pressure on the common bile duct interfered with excretion of bile from the liver. Even minor degrees of obstruction of the common bile duct can result in an elevation of the alkaline phosphatase. It is difficult to select between metastatic neoplasm to the bones and pressure on the bile duct, but I prefer to associate the deformity of the duodenal bulb with enlargement of the lymph nodes in that area and I shall hypothesize that enlarged lymph nodes also exerted pressure on the common bile duct, interfering with bile excretion and accounting for the elevation of the alkaline phosphatase.

After reviewing this extensive amount of laboratory work I come back to the diagnosis that was suggested by the present illness — namely, a malignant neoplasm. It seems to me that there is no evidence of a carcinoma, but there is evidence of involvement of retroperitoneal lymph nodes — one of which was probably pressing on the kidney and another on the duodenum. It seems to me that the patient had a lymphoma or myeloma. In the presence of 20 per cent plasma cells in the bone marrow it would be very rash not to consider seriously multiple myeloma so that will be my first diagnosis. For a second choice I shall consider the Hodgkin type of lymphoma.

Dr. Alfred Kranes: In view of the elevated alkaline phosphatase I should think an equally good possibility would be metastatic carcinoma to the liver, presumably from a pancreatic lesion. There was no obvious bone disease, or other reason for a high alkaline phosphatase.

Dr. Charles H. DuToit: The patient had a slightly increased total protein, with some increase in the alpha$_2$ and gamma globulins. I might comment on the general diagnostic usefulness of paper electrophoresis. In a few conditions such as multiple myeloma, advanced liver disease and nephrosis there are clear-cut patterns; none of these were present in the case under discussion. There is nothing in this pattern to suggest multiple myeloma. Unfortunately, in other diseases, including chronic infection, lymphoma, leukemia, Hodgkin's disease and some of the connective-tissue diseases, there is so much overlapping of changes that the pattern is not usually diagnostic.

Dr. Scully: Dr. Jacobson, you saw this patient; will you tell us your opinion?

Dr. Bernard Jacobson: This patient had a marked thrombocytosis, which was confirmed by the finding of increased numbers of megakaryocytes in the very adequate bone-marrow smears. In addition there was a well defined increase in normal mature plasmacytes. Among the various causes of thrombocytosis, the commonest is chronic or acute blood loss. Yet the protocol contains nothing to suggest blood loss in the immediate past. Among the other causes of thrombocytosis is sepsis. Sepsis itself will sometimes produce a stimulus to the megakaryocytes and increase the number of platelets. It has been known for a long time that Hodgkin's disease will sometimes cause increased numbers of megakaryocytes, usually with an increase in the thrombocytes in the peripheral blood. When we saw the mature plasmacytes we were reasonably certain it was not multiple myeloma, but a reactive plasmacytosis. Unfortunately, that is not in itself diagnostic because in large series of bone-marrow examinations, we can find a significant increase in plasmacytes of the mature variety, up to 25 per cent, in various types of chronic infections like tuberculosis and brucellosis; in any type of granuloma like sarcoidosis; in lymphomas; in some of the

group diseases; and in a host of conditions, including many hypersensitivity or allergic phenomena. The plasma cells are probably the seat of the formation of antibody of a certain variety, and of the increased abnormal globulin that appears in the peripheral blood.

We were left with nonspecific conclusions, but the combination of fever, thrombocytosis and an increased number of mature plasma cells in the bone marrow suggested to me that the diagnosis was lymphoma rather than infection or other conditions.

A PHYSICIAN: May I ask why a bone-marrow biopsy was done after the aspiration?

DR. JACOBSON: It was done because of the suggestion of lymphoma; we thought we might pick up lymphoma more accurately than in an aspiration smear.

A PHYSICIAN: But you did not think it was a myelophthisic anemia?

DR. JACOBSON: The appearance of the peripheral blood did not suggest myeloid metaplasia or myelophthisic anemia.

CLINICAL DIAGNOSIS

Retroperitoneal lymphoma.

DR. VICTOR G. BALBONI'S DIAGNOSIS

Multiple myeloma; ? Hodgkin's disease.

ANATOMICAL DIAGNOSIS

Renal-cell carcinoma.

PATHOLOGICAL DISCUSSION

DR. SCULLY: The operation was an exploration of the mass in the region of the right kidney. The lower pole of the kidney was found to be completely replaced by a tumor 8 cm. in diameter; on section this had the typical variegated picture of a renal-cell carcinoma. There was invasion of the renal vein. The patient has been followed postoperatively for about five weeks: his temperature has returned to normal, and his strength and appetite have increased.

This is one of the unusual cases of renal-cell carcinoma that manifest themselves only by nonspecific symptoms such as anemia and fever. There have been a number of reports in the literature of similar cases. One article on this general subject was appropriately entitled, "Confusing clinical manifestations of malignant renal neoplasms."[1] Clarke and Goade[2] recently studied 36 cases of renal-cell carcinoma verified at operation. Ten of the patients had fever, and in 2 it was the chief complaint. The fever disappeared after nephrectomy in all patients except 1 who had hepatic metastases. Nine of the 36 patients had a significant degree of anemia preoperatively; this responded to transfusions and nephrectomy in the cases in which all the tumor appeared to be removed.

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2. Clarke, B. G., and Goade, W. J., Jr. Fever and anemia in renal cancer. *New Eng. J. Med.* **254**:107-110, 1956.

BOOKPLATE COLLECTION OF THE BOSTON MEDICAL LIBRARY

12. Bookplate of John Homans, II, nephew and namesake of the ovariotomist. Dr. Homans, known as "Young John" by his friends, to distinguish him from his eminent uncle, was a member of the Executive Committee of the Boston Medical Library from 1892 to 1902.

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JOINT COMMISSION ON MENTAL ILLNESS AND HEALTH

INTEREST in mental-health functions in the fields of health promotion, outpatient treatment, better management of patients in the hospital and expansion of the rehabilitation services available has spread rapidly since World War II. The great public interest in mental health and the demand for improved service have sorely taxed available training and clinical resources. Many new organizations and new professional groups are now participating in the care of the mentally ill. For example, psychologists in increasing numbers lend their services to the operation of clinics and hospital treatment programs. Social scientists in ever-increasing numbers study the structures of the hospital and clinic programs and make appropriate researches and recommendations. Most schools of theology instruct students in pastoral counseling. Counseling and therapy by social workers in family-service agencies are a matter of routine practice. Most public-school systems have installed psychologic and counseling services. Most family physicians and pediatricians are expected to be able to handle minor mental-health problems and to contribute to the over-all knowledge and education of families asking questions in this area. The mental-health aspects of the whole problem of aging and those of industry are objects of study with planned expansion in services.

The nineteen organizations that have joined with the American Psychiatric Association and American Medical Association to form the Joint Commission on Mental Illness and Health are to be commended for the timeliness of their organization of a survey to assess present practices and the role of the various professional groups, and to make suggestions for new developments. They will also make recommendations for possible better use of existing resources. Since the Joint Commission and its membership represent the major professional groups, in both the medical and paramedical professions, it seems assured that the study will be a broad one and representative of the best thoughts and efforts in this field. The federal Government is to be congratulated on providing funds to help carry out this study. It is hoped that the foundations will make additional funds available.

The headquarters of the Joint Commission Study will be at 808 Memorial Drive in Cambridge, Massachusetts. A staff for the project is being selected. Dr. Jack R. Ewalt, Massachusetts Commissioner of Mental Health, will go on a part-time basis in the Department of Mental Health, principally by relieving himself of the details of his administrative position, and direct the project. The associate director will be Fillmore Sanford, Ph.D., executive secretary of the American Psychological Association, who is now working part time on the project and is gradually withdrawing his functions from the American Psychological Association and plans to be full time on or about June 1. In the social sciences, Gordon Blackwell,

Ph.D., of the University of North Carolina, is serving as a chief consultant at a staff level. Large numbers of advisory persons, all distinguished people in their respective professions, will offer suggestions on the details and directions of the study.

The officers of the association are Dr. Kenneth Appel, of Philadelphia, president of the Joint Commission; Dr. Leo Bartemeier, of Baltimore, Maryland, chairman of the Board of Trustees; and Mr. Charles Schlaifer, of New York City, secretary-treasurer; Nicholas Hobbs, Ph.D., of Nashville, Tennessee, will be vice-chairman of the Board of Trustees, and Brewster Smith, Ph.D., will be vice-president.

The study should take approximately three years.

DISPERSION OF NATURAL KNOWLEDGE

At a meeting on November 30, 1955, commemorating the three-hundred-and-tenth anniversary of the Royal Society of London, — the president of the Academy of Sciences of the United Soviet States of Russia and colleagues being present, — Lord Adrian, O.M., at the completion of his five-year term in office, delivered the farewell presidential address. His text, as reported in the *British Medical Journal* on December 10 was developed around the question of how the Royal Society could best fulfill its original purpose of "Improving Natural Knowledge."

The Society's present fields of activity are broad, including the dispensing of grants, awards and medals, the publication of journals and the holding of meetings; but the retiring president expressed his belief that its really important function is to exist and to perpetuate its existence by the election of new fellows. In view of so much highly differentiated specialization as there is today, finding its voice in so many special meetings and the publication of so many specialized periodicals, the meetings and publications of the Royal Society are of relatively less basic importance than in the earlier centuries of its existence. A new value, however, pertains to its activities through which specialists may present their material "before an audience of fellow scientists who are not all fellow specialists." This need of intercommunication becomes more acute with the increasing development of special skills and even of special vocabularies. A great need has come into being for the interpretation of the work performed in a number of fields so that the resulting knowledge may be usefully integrated.

In England as in this country a certain degree of pressure is put on institutions of learning and of research to deal too much with classified material at the risk of losing some of that "winnowing breeze of freedom" that keeps the mind refreshed. The need exists more than ever of remaining independent of the State, even while co-operating with it. Lord Adrian's recommendation was that the Society should act only as an adviser and not as an administrator. His final injunction comes close to constituting an aphorism — that responsibilities must not be allowed to increase at the cost of the leisure to survey them.

The Royal Society, although chartered under its present name in 1662, was established as the "Invisible College" in 1645. A hundred and thirty-five years later, but still representative of the hunger for knowledge that the Renaissance had brought about, the American Academy of Arts and Sciences was founded in Boston. Its design, more diffusely stated than that of the Royal Society, was "to cultivate every art and science which may tend to advance the interest, honor, dignity, and happiness of a free, independent, and virtuous people." Virtue was apparently more of a factor in the self-determining colonies at the close of the American Revolution than in England during the reign of Charles II.

As with its illustrious prototype the Academy still aims in its meetings at "appealing to a wider group than the speakers' fellow specialists"; in support of this generalization it has seemed desirable that its somewhat ponderous *Proceedings* might be restricted to articles of general interest among educated persons. In this country, too, special journals enough exist for the publication of the results of highly specialized investigative procedures.

The search for a title to the new proceedings ended, unlike the hunting of the snark, with a solid reward for the committee's pains, for there came soon to mind the name of the world's first great general specialist — Daedalus — artist, architect, artificer, engineer and pioneer bird man, inventor of the ax, the auger and the plummet, contriver of masts, spars (and possibly the sails to spread on them), and designer of the Cretan labyrinth. Under the title *Daedalus,* the *Proceedings,* new and refreshed, although continuing with the consecutive volume number 86, should prove attractive not only to the Academy's various classes of fellows but also to general readers outside the Academy.

MEDICAL EDUCATION WEEK

The use of a designated week to publicize and dramatize a cause is now an accepted and often successful method of promotion.

Although there are more weeks so dedicated than there are weeks in a year, those that are carefully planned and executed and promote a sound and reasonable cause do attract national attention. This attention may be fleeting, but it is attention that otherwise may not be forthcoming.

Of particular interest to the medical profession is the week of April 22, which, under the sponsorship of the American Medical Association, Association of American Medical Colleges, National Fund for Medical Education and American Medical Education

Foundation, has been designated and will be so promoted as Medical Education Week.

The purposes of this special week are to call national attention to the significance of medical education and the problems of medical schools, to bring home to the public the contributions of medical science to American life, and to foster public interest in the private support of medical education.

Through the educational campaign, the Week's sponsors hope to dispel such myths as the one that medical-school graduates are not keeping pace with the population growth, that medical schools try to keep their enrollments as small as possible, that they refuse admission to a vast number of applicants, that only "A" students are admitted to them and that the American Medical Association attempts to restrict the number of physicians.

Emphasis will also be placed on the financial problems of medical education, and the need by medical schools (now operating on a budget of over $159,000,000) of an additional $10,000,000 yearly to broaden their teaching activities, particularly in the fields of psychiatry, rehabilitation, geriatrics and nuclear physics.

In a letter to Dr. Elmer Hess, president of the American Medical Association, President Eisenhower states:

> Our eighty-one medical schools are the sole source of supply for the physicians needed, in increasing numbers, to meet the requirements of our growing population. These schools have a major role in the advancement of medical science through research and the training of medical scientists and research workers. Their third major function is provision of patient care.
>
> I earnestly hope that Medical Education Week will bring the American people a clearer recognition of this threefold mission of the medical schools and pay rich dividends in increased public understanding and support.

The *Journal*, too, earnestly hopes that Medical Education Week will accomplish the aims of its sponsors.

CAPTAINS OF THESE MEN–

A NEW Army policy effective in February of this year provides for the advancement to the temporary grade of captain of all Army physicians and dentists who have had at least one year of professional experience. The "year of professional experience" is not defined, but it may presumably consist, for physicians at least, of a year's internship or residency after graduation from medical school. The only first lieutenants remaining in the Army Medical Corps will henceforth be military interns.

The advancements, according to a release from the Surgeon General's office, will affect an estimated 1100 medical and 500 dental first lieutenants without impeding the promotion of nonmedical officers, since the Department of Defense has authorized that the advancements be made outside the Army's established quota of captains. As of April, physicians and dentists freshly entering the Army after a year of professional experience will be commissioned as captains from the start of their service.

The new policy, the Department states, takes into account the nine years that must elapse after graduation from high school before physicians are prepared to practice their profession. Their prolonged educational requirements are contrasted with the usual four years of formal education to which most other officers are subjected before their initial commissioning. This elevation of a grade in rank with its commensurate pay increase may add glamor to the Army as a career, especially in view of the varied types of practice that such a career now affords.

There seems little reason, at the moment of writing, to anticipate any disbanding of the world's armies in the immediate future, or of any impending disarmament race of sufficient magnitude to throw an appreciable number of unemployed military surgeons on the town.

Ninth Annual Meeting of the American Medical Association. — *We are requested by Dr. Wm. Brodie, of Detroit, one of the secretaries, to state that the next meeting of this Association will be held in Firemen's Hall, corner of Jefferson Avenue and Randolph street, in that city . . . Medical journals please copy.*

Boston M. & S. J., *March 27, 1856*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

ANESTHETIC DEATH

A twenty-six-year-old gravida II, para I, had a normal prenatal course and went into spontaneous active labor about three weeks before term. She died less than an hour after admission.

She was admitted to the hospital in active labor at about 3:00 a.m., when the cervix was fully dilated, with the vertex in the left occipital anterior position. There was scarcely time for obstetric preparation when the membranes ruptured spontaneously fifteen minutes later, and the patient was rushed to the delivery room, where open drop ether was started with the patient in lithotomy position and the baby's head visible. A mid-line episiotomy was done, and the infant easily delivered by Ritgen's maneuver. With the

expulsion of the baby's feet, the patient vomited. This was exactly seven minutes after the onset of ether anesthesia, which was then stopped and the oropharynx aspirated with the patient in Trendelenburg position. During the next eight minutes she became progressively more cyanotic, with a failing pulse and blood pressure.

Thus far, anesthesia had been given by a competent trained nurse anesthetist, who now called the attending staff anesthetist. He arrived very promptly approximately twenty minutes after the onset of anesthesia and twelve and a half minutes after the initial vomiting. He was able to intubate the patient immediately, finding the oropharynx filled with gastric contents and several large pieces of solid material in the trachea. An endotracheal suction tube was inserted but encountered an impassable solid object near the tracheobronchial junction. For this reason it was believed that tracheotomy would be valueless. The solid material was later found to be a large fragment of meat that the patient had eaten two hours before admission. Further efforts at aspiration and resuscitation failed, and she was pronounced dead.

This was classified as a preventable death — an almost automatic classification for all anesthetic deaths since she would have done very well indeed either with no anesthesia or with a low spinal anesthesia.

However, it is easy to imagine that she was admitted to the hospital in labor and in obvious, extreme distress, for she was transferred to the delivery room with the cervix fully dilated and the head probably crowning. It is easy to imagine that no one inquired the time of her last meal. She may have been unwilling or unable to tell the truth about this. It is also easy to visualize a hasty request for "a few drops of ether" as rapidly as possible to prevent precipitate, painful delivery. These are, of course, the exact circumstances that encourage the kind of tragic accident that actually occurred.

Such deaths can be prevented by education of every patient to avoid food when labor is suspected, scrupulous questioning of every patient admitted to the hospital, regardless of the activity of labor, and at least some minimal form of premedication twenty or thirty minutes before induction of anesthesia.

JOHN FIGGIS JEWETT, M.D.
Chairman

DEATH

HAMILTON — Frank A. Hamilton, M.D., of Boston, died on February 12. He was in his seventy-seventh year.

Dr. Hamilton received his degree from Harvard Medical School in 1906. He was an instructor in anatomy at Harvard Medical School and a fellow of the American Medical Association.

He is survived by his widow, one son and a daughter.

CORRESPONDENCE

MOUNT AUBURN HOSPITAL CONTROVERSY

To the Editor: So much discussion has arisen over the problems at the Mount Auburn Hospital, that readers of the *Journal* might be interested in a condensed statement of the facts in the case, as I interpret them from the point of view of the staff.

At the start, it should be said that the controversy involves a matter of principle, not of personalities. It arises from the action of the trustees in arbitrarily revoking the existing bylaws of the staff, and imposing a new set of bylaws without the consent or approval of the staff. The trustees take the position that their authority is absolute and final, and that the opinion of the staff does not have "much if any relevance," to quote from a letter of the chairman of the Board of Trustees. Obviously, if this interpretation prevails, the medical profession at large will occupy a wholly subordinate position in the hospitals where they give their services.

In opposition to the trustees' concept, the members of the staff believe that they are entitled, as physicians, to democratic representation in managing their own affairs. Self-government has, in fact, been guaranteed to them by the Joint Commission for Accreditation of Hospitals, as categorically stated in *Standards for Hospital Accreditation*, issued in April, 1953, and reaffirmed in the August, 1953, *Bulletin of the Joint Commission*. Furthermore, the regulations of the Massachusetts Department of Public Health contain a similar requirement, as currently published in the *Licensure Rules and Regulations*, stating that "The medical staff shall be an organized group which shall initiate and, with the approval of the governing body of the hospital, adopt by-laws . . ." By the staff's interpretation, therefore, the action of the trustees violates these regulations as well as the principle expressed by joint medical societies.

The matter came to a head on September 28, 1955, when the trustees terminated the existing bylaws of the staff, which had been originally issued in 1946 with trustee approval and which had been operating satisfactorily for eight years. The trustees then adopted bylaws for the staff, and ordered that they become effective two days later, allowing a transition period for the change-over. These bylaws were not actually published to the staff until October 17. Consequently, they were technically in effect more than two weeks before the staff had received copies of them. It would be difficult to imagine a more flagrant example of arbitrary imposition of regulations, or of withholding from the staff the privilege of approving their provisions. This action stands in startling contrast to provisions in the Joint Commission's *current* standards, which lists as an "absolute prerequisite" that the active staff shall "perform all the organizational duties pertaining to the medical staff," including "organization of its government."

As further evidence of the unyielding attitude of the trustees in issuing these bylaws, it should be pointed out that they rejected the so-called McKittrick provision for conciliation and appeal of grievances. This had been recommended and adopted by the staff in the final draft of new bylaws. The provision is one that had been worked out with great care by Dr. Leland S. McKittrick and had been adopted, through his efforts, by both the Massachusetts Medical Society and the Massachusetts Hospital Association. It provided an impartial tribunal, consisting of equal representation from both organizations, where grievances could be reviewed and adjusted. The trustees did not vouchsafe any reason for its repudiation.

The reaction of the staff to the trustees' action was expressed at the scheduled staff meeting on November 1, 1955, when the new bylaws were fully and openly debated. A secret ballot was taken, and the vote was 54 to 18 in favor of *withholding* approval of the new bylaws, and of sending a committee to the trustees for discussing some possibility of working out a compromise. It seems unnecessary to comment that in this country a majority vote is decisive; a two-to-one majority, emphatically decisive; and a three-to-one majority, overwhelmingly decisive. The extent of the staff's opposition to the new bylaws may be measured by this vote.

As directed by the staff, a committee was appointed to meet with the trustees for discussion of compromise proposals. A letter from the president of the staff, requesting such a meeting, was answered by the following threat of coercive action from Mr. Ames, chairman of the Board of Trustees:

> Indeed, any further delay on the part of any Chief of Service, Committee Chairman, or other officer or member of the Staff in performing his obligations under the new [Trustee-imposed] by-laws could only be considered as an indication that the individual concerned is one who does not intend to abide by and comply with the established policies of the hospital. It is obvious there can be no place on the staff for any such individual.

Mr. Ames agreed to a conference with the proviso that "any discussion, however, must proceed on the basis that the new [trustee-imposed] by-laws are in effect, and will be observed in their present form until such time as they may be amended in accordance with the stated amendment procedure." The conference was held, but compromise proposals made by the staff were rejected, and no counterproposals were received from the trustees. At the annual meeting of the staff, it was voted, 51 to 18, to refer the matter to the Massachusetts Medical Society for whatever action might be necessary to restore to the staff its rights as a self-governing body.

In conclusion, it may be said that the members of the staff of the Mount Auburn Hospital believe that the issue of professional independence is an extremely important one that affects doctors everywhere. There is urgent need for taking steps to obtain and preserve the principle of self-government for all hospital staffs throughout the State.

CHARLES H. BRADFORD, M.D.

Boston

BOOK REVIEW

Wiederherstellung des Harnweges und kunstliche Harnableitung bei Erkrankungen des Harnleiters: Indikationen und Methoden. By Prof. Dr. H. Boeminghaus, Düsseldorf. 8°, paper, 60 pp., with 53 illustrations. Stuttgart: Georg Thieme, 1955. DM 15.-$3.60. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

The author has drawn on his experience and the literature (principally European) for a discussion of ureteral injuries, fistulas, stenoses, both congenital and acquired, including ureteropelvic-junction obstructions, atonic states of the ureter, ureteral tumors and ureteral reflux due to insufficiency of the ureterovesical valves.

Treatment recommended for ureteral injuries is quite conventional — primary repair if possible, reimplantation in the bladder, and otherwise bladder-flap tube repairs for lower ureteral defects, ileal-segment substitution between the cut end of the ureter and bladder for long or nearly complete defects, ileal replacement of the bladder after cystectomy (an ileal segment into which ureters are implanted and sutured to the apex of the prostate or membranous urethra), an ileal segment into which the ureters have been implanted pulled through the rectal sphincter to the perineal skin with intact large bowel. Conventional ureterosigmoidostomy is mentioned but not favored as a means of urinary diversion. Cutaneous ureterostomy and nephrostomy are recommended only when no other solution seems possible for preservation of renal function.

Ureteropelvic-junction obstructions are treated by plastic repair. Lateral anastomosis, side-to-side anastomosis, division and reimplantation of the ureter into the renal pelvis, division and splinting of strictures are discussed and illustrated, but no mention is made of the Foley Y-plasty, which has been used extensively and effectively in this country, and though the author, in effect, recommends the Davis intubated-ureterostomy technic for long strictures of the ureter, he does not mention Dr. Davis's articles.

The discussion of ureteral atony is largely theoretical and makes no mention of the recent work of Swenson and others in this country that provides a good basic explanation for the development of so called megaloureter. Treatment recommended does not seem physiologically sound or convincing. Technics for reimplantation of the lower ureter into the bladder either for stricture or for reflux appear effective. Nephroureterectomy is advised for ureteral tumors.

Although this article is well written and illustrated, the therapy recommended is not completely up to date.

WYLAND F. LEADBETTER, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Atlas of General Surgery. By Joseph R. Wilder, M.D., assistant professor of surgery, New York Medical College, Flower and Fifth Avenue Hospitals, and assistant attending, Metropolitan Hospital and the Bird S. Coler Hospital, New York City. F°, cloth, 222 pp., with 101 plates. St. Louis: The C. V. Mosby Company, 1955. $13.50.

German-English Medical Dictionary. By W. O. Goulden, B.A. (Hons), Dr.phil. 8°, cloth, 513 pp. Boston: Little, Brown and Company, 1955. $10.00.

Subacute Bacterial Endocarditis. By Andrew Kerr, Jr., M.D., assistant professor of medicine, Louisiana State University School of Medicine, and visiting physician, Charity Hospital of Louisiana, New Orleans. 8°, cloth, 343 pp., with 7 illustrations, 2 charts, and 1 table. Springfield, Illinois: Charles C Thomas, 1955. $6.50. (Publication No. 274, *American Lecture Series.*)

From Custodial to Therapeutic Patient Care in Mental Hospitals: Explorations in Social Treatment. By Milton Greenblatt, M.D.; Richard H. York, Ph.D.; and Esther Lucile Brown, Ph.D. In collaboration with Robert W. Hyde, M.D. 8°, cloth, 497 pp. New York: Russell Sage Foundation, 1955. $5.00.

Pharmacopoea Internationalis. Vol. 2. 8°, cloth, 350 pp., with illustrations and tables. Geneva: World Health Organization, 1955. $6.75. (Published also in French.) (Distributed in the United States by Columbia University Press, New York City.)

A Textbook of Clinical Pathology. Edited by Seward E. Miller, M.D., medical director, United States Public Health Service, and chief, Division of Special Health Services, Washington, D.C. Fifth edition. 8°, cloth, 1208 pp., with illustrations and tables. Baltimore: The Williams and Wilkins Company, 1955. $11.00.

Classification for Medical Literature. By Eileen R. Cunningham, librarian and professor of medical library science, Vanderbilt University School of Medicine. With the collaboration of Eleanor G. Steinke, assistant librarian, Vanderbilt University School of Medicine. Fourth edition, revised and enlarged. 8°, paper, 164 pp. Nashville: Vanderbilt University Press, 1955. $2.75.

Leonardo the Anatomist. By Elmer Belt, M.D. 8°, cloth, 76 pp., with illustrations. Lawrence, Kansas: University of Kansas Press, 1955. $2.00. (Fourth series, *Logan Clendening Lectures on the History and Philosophy of Medicine.*)

Leitfaden der Urologie: Für Studium und Praxis. By Prof. Dr. C.-E. Alken, director, Urologische-Universitätsklinik, Homburg/Saar. 8°, paper, 164 pp., with 79 illustrations. Stuttgart: Georg Thieme, 1955. $3.95. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Applied Medical Bibliography: For students. By William Dosite Postell, medical librarian and professor of medical bibliography, Louisiana State University School of Medicine, New Orleans. 8°, cloth, 142 pp., with 12 illustrations and a frontispiece. Springfield, Illinois: Charles C Thomas, 1955. $4.50. (Publication No. 259, *American Lecture Series.*)

Splenin A in Rheumatic Fever: The testing of splenin A as an anti-inflammatory agent. By Alvin F. Coburn, M.D.; Lucile V. Moore, M.D.; Judith Wood, M.D.; and Mary Roberts, R.N. (From The Rheumatic Fever Research Institute, Northwestern University Medical School.) 8°, cloth, 87 pp., with 5 illustrations. Springfield, Illinois: Charles C Thomas, 1955. $3.75.

Textbook of Occupational Therapy: With chief reference to psychological medicine. By Eamon N. M. O'Sullivan, M.B., D.P.M. 8°, cloth, 319 pp., with 18 illustrations. New York: Philosophical Library, Incorporated, 1955. $10.00.

Medical and Psychological Teamwork in the Care of the Chronically Ill: Reports and discussions of a conference held March 28-31, 1954, at Galveston, Texas under the auspices of the Josiah Macy, Jr., Foundation of New York City, and the University of Texas Medical Branch. Edited by Molly Harrower, Ph.D., research and consulting psychologist, New York, New York. 8°, cloth, 232 pp. Springfield, Illinois: Charles C Thomas, 1955. $5.75. (Publication No. 276, *American Lecture Series.*)

The Expression of the Emotions in Man and Animals. By Charles Darwin, M.A., F.R.S. With a preface by Margaret Mead. 8°, cloth, 389 pp., with illustrations. New York: Philosophical Library, 1955. $6.00.

Understanding Surgery. Edited and compiled by Robert E. Rothenberg, M.D., associate attending surgeon, Jewish Hospital, Brooklyn, and clinical assistant professor of environmental medicine and community health, State University College of Medicine, New York. 16°, paper, 620 pp., with 101 illustrations by Sylvia and Lester V. Bergman. New York: Pocket Books, Incorporated, 1955. 50 cents.

Whys and Wherefores in Tuberculosis. By George Day, M.A., M.D. 16°, paper, 44 pp. London: Tavistock House North, 1955. 3s. 6d. (The National Association for the Prevention of Tuberculosis.)

Your Feet and Their Care. By William A. Rossi, doctor of surgical podiatry. With an introduction by Dr. Joseph Lelyveld, chairman, National Foot Health Council. 8°, cloth, 212 pp., with 48 illustrations. New York: Emerson Books, Incorporated, 1955. $3.00.

Peptic Ulcer: Diagnosis and treatment. By Clifford J. Barborka, M.D., M.S., D.Sc., associate professor of medicine and chief, Gastrointestinal Clinics, Northwestern University Medical School, attending physician, Passavant Memorial Hospital, and senior consultant in Gastroenterology, Veterans Administration Research Hospital, Chicago; and E. Clinton Texter, Jr., M.D., associate in medicine and assistant chief, Gastrointestinal Clinics, Northwestern University Medical School, attending physician, Passavant Memorial Hospital, and attending physician in gastroenterology, Veterans Administration Research Hospital, Chicago. 8°, cloth, 290 pp., with 33 illustrations. Boston: Little, Brown and Company, 1955. $7.00.

Anesthesia in Ophthalmology. By Walter S. Atkinson, M.D., associate clinical professor of ophthalmology, New York University Post-Graduate Medical School and House of the Good Samaritan, Watertown, New York. 8°, paper, 101 pp., with 44 illustrations. Springfield, Illinois: Charles C Thomas, 1955. $3.25. (Publication No. 251, *American Lecture Series.*)

Introduction to Virology. By Gilbert Dalldorf, M.D., director, Division of Laboratories and Research, New York State Department of Health, Albany, New York. 8°, cloth, 102 pp., with 6 illustrations and 4 tables. Springfield, Illinois: Charles C Thomas, 1955. $3.50.

The Health of the Elderly at Home: A medical, social and dietary study of elderly people living at home in Sheffield. By William Hobson, B.Sc., M.D., D.P.H., professor of social and industrial medicine, University of Sheffield; and John Pemberton, M.D., M.R.C.P., senior lecturer in social and industrial medicine, University of Sheffield. In collaboration with E. R. Bransby, M.Sc., Ph.D.; H. Droller, M.D., M.R.C.P.; Cissie Roseman, B.Sc.; and D. L. Woodhouse, Esq. With a foreword by Lord Horder, G.C.V.O., M.D., F.R.C.P. 8°, cloth, 238 pp., with 12 illustrations and 82 tables. London: Butterworth and Company, Limited, 1955. 30 s.

Child Behavior. By Frances L. Ilg, M.D., director, Gesell Institute of Child Development; and Louise Bates Ames, Ph.D., director of research, Gesell Institute of Child Development. 8°, cloth, 364 pp. New York: Harper and Brothers, 1955. $3.95.

Obstetrical Roentgenology. By Robert Berman, M.D., assistant clinical professor of obstetrics and gynecology, New York University College of Medicine, attending obstetrician and rotating director of obstetrics and gynecology, Beth Israel Hospital, Newark, New Jersey, associate in roentgenology, Margaret Hague Maternity Hospital, Jersey City, New Jersey, assistant attending in obstetrics and gynecology and director of Sterility Clinic, University Hospital, New York City, and consultant obstetrician and gynecologist, Irvington General Hospital, Irvington, New Jersey. 8°, cloth, 599 pp., with 486 illustrations. Philadelphia: F. A. Davis Company, 1955. $12.50. (*Obstetrics and Gynecology: A series of monographs.* Edited by Claude E. Heaton, M.D.)

NOTICES

AERO MEDICAL ASSOCIATION

The annual meeting of the Aero Medical Association will be held at the Drake Hotel, Chicago, Illinois, April 16-18. One hundred and thirty-seven papers will be presented dealing with every aspect of the field and coming from military and civilian sources in nine countries. The section meetings will include panel discussions of vital topics by leading authorities in each field. The Wives Wing of the Aero Medi-

cal Association will hold its functions on the same dates. Further information may be obtained from Dr. James N. Waggoner, Arrangements Committee, Central Office, Aero Medical Association, P.O. Box 26, Marion, Ohio.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The American Board of Obstetrics and Gynecology announces that the next scheduled examination (Part II), oral and clinical, for all candidates will be held at the Edgewater Beach Hotel, Chicago, Illinois, May 11-20. Formal notice of the exact time of each candidate's examination will be sent in advance of the examination dates. Candidates who participated in the Part I examinations will be notified of their eligibility for the Part II examinations as soon as possible.

SOCIETY MEETINGS AND CONFERENCES

MARCH 22. American Academy of General Practice. Page 1092, issue of December 15.
MARCH 22 and 23. New England Conference on Human Nutrition. Page 539, issue of March 15.
MARCH 22 and 23. New England Medical and Dental Symposium. Page 347, issue of February 16.
MARCH 22–28. Consultation Clinics for Crippled Children in Massachusetts. Page 440, issue of March 1.
MARCH 22–28 and JUNE 4–13. Army Medical Service Postgraduate Course. Page 84, issue of July 14.
MARCH 24 and 25. American Psychosomatic Society. Page 491, issue of March 8.
MARCH 26. Massachusetts Heart Association. Page 539, issue of March 15.
MARCH 27 and APRIL 3. Boston City Hospital House Officers' Association. Page 297, issue of February 9.
MARCH 28. Massachusetts Society of Examining Physicians. Page 539, issue of March 15.
MARCH 28 and APRIL 18. Greater Boston Medical Society. Page 208, issue of August 4.
APRIL 2. Fried Lecture Series. Page 535, issue of September 22.
APRIL 2. Benjamin Waterhouse Medical History Society. Page 539, issue of March 15.
APRIL 2 and 16. Hartford Medical Society. Page 242, issue of February 2.
APRIL 3. Third Microcirculatory Conference. Page 399, issue of February 23.
APRIL 4. New England Surgical Society. Page 347, issue of February 16.
APRIL 5. Second Annual Symposium on Cardiovascular Disease. Page 490, issue of March 8.
APRIL 6. Massachusetts Society of Anesthesiologists. Page 539, issue of March 15.
APRIL 7. American Congress of Physical Medicine and Rehabilitation. Page 491, issue of March 8.
APRIL 8. American College of Gastroenterology. Page 491, issue of March 8.
APRIL 12. Nu Sigma Nu Fraternity. Page 491, issue of March 8.
APRIL 15–20. American College of Allergists. Page 399, issue of February 23.
APRIL 16–18. Areo Medical Association. Page 585.
APRIL 16–21. American Academy of Pediatrics. Page 399, issue of February 23.
APRIL 23–26. International Academy of Proctology. Page 399, issue of February 23.
APRIL 25. Massachusetts Heart Association. Page 490, issue of March 8.
APRIL 26. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.
MAY 1–5. Sixth National Congress on Pediatrics. Page 491, issue of March 8.
MAY 2. Postgraduate Medical Institute. Page 487, issue of September 15.
MAY 3–5. American Goiter Association. Page 348, issue of August 25.
MAY 14–18. American Nurses' Association. Page 491, issue of March 8.
MAY 28–JUNE 1. European Symposium on Vitamin B. Page 578, issue of September 29.
JUNE 1–9. International Medical-Surgical Meetings. Page 540, issue of March 15.
JUNE 21–23. Society of Nuclear Medicine. Page 1092, issue of December 15.
JUNE 21–24. American Academy of Dental Medicine. Page 944, issue of December 1.
AUGUST 19–23. American College of Chest Physicians. Page 840, issue of November 10.
SEPTEMBER 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
SEPTEMBER 10–14. American Dietetic Association. Page 1180, issue of December 29.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, MARCH 29

THURSDAY, MARCH 29
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*11:15 a.m. Thoracic Conference. Cardiac Resuscitation: Policies for general hospitals. Dr. Dwight E. Harken, Main Amphitheater, Peter Bent Brigham Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Staff Conference. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, MARCH 30
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*1:00–3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, MARCH 31
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Benjamin Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference (Blood Clinic). Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, APRIL 2
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. William Schwartz. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Recovery-Room Statistics. Dr. Galla. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.

(Concluded on page xxiv)